Development of 1,4-Benzodiazepine Cholecystokinin Type B Antagonists†

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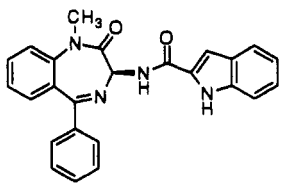
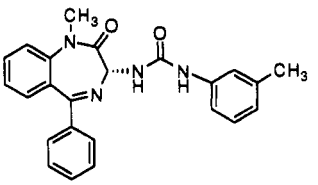
A series of 3-(arylureido)-5-phenyl-1,4-benzodiazepines, nonpeptidal antagonists of the peptide hormone cholecystokinin (CCK), are described. Derived by reasoned modification of the CCK-A selective 3-carboxamido-1,4-benzodiazepine, MK-329, this paper chronicles the development of potent, orally effective compounds in which selectivity for the CCK-B receptor subtype was achieved. The principal lead structure that emerged from these studied is L-365,260, a compound which has been submitted for clinical evaluation. Details of the ability to modulate the receptor interactions of these benzodiazepines by appropriate structure modifications are discussed which imply the possibility of further refining the CCK-B receptor affinity and selectivity of this class of compounds.

In an earlier communication we disclosed our initial results on the discovery of benzodiazepine structures that are potent antagonists of the peptide hormones cholecystokinin (CCK) and gastrin.[1] The significance of these compounds is that they were the first small molecule, nonpeptides to exhibit selectivity for the CCK-B versus the CCK-A receptor subtype and thus provided further confirmation for the existence of two CCK receptor types.[2] Concomitantly, our results lent additional support to the notion that effective, non-peptide ligands for peptide receptors can be constructed by structural adjustment of the benzodiazepine core.[3]

The forebear of the reported series of CCK-B selective 1,4-benzodiazepines is the CCK-A selective 3-carboxamido-1,4-benzodiazepine MK-329, 1.[4] This substance has been under investigation as a potential therapeutic agent for the treatment of irritable bowel syndrome.[5] The principal lead structure that emerged from our preliminary study on CCK-B selective compounds, L-365,260 (2) is in the early stages of clinical development as a potential ameliorator of anxiety disorders.[6]



1, MK-329



2, L-365,260

The purpose of this report is to give a fuller accounting of the process which led to the development of the CCK-B selective antagonist **2**. In this paper we present the synthesis and structure/activity profile of a collection of 3-ureido-1,4-benzodiazepines accenting the empiricism and logic by which selectivity in binding to the CCK-B receptor was achieved with this class of compounds.

Chemistry

The structures of the 3-ureido-1,4-benzodiazepines which comprise this report are presented in Tables II–IV and fall into three broad categories: 3-ureido-1,4-benzodiazepines with N^1-methyl substituents, analogs wherein the N^1-substituent is absent or larger than methyl, and heteroaryl derivatives. The compounds collated in Tables II–IV were prepared according to the general processes outlined in Schemes I–VI; these schemes and the general methods therein are cross-referenced in Tables II–IV.

The syntheses of the key intermediates **Ia**, **Ib**, **IIa**, and **IIb** (Scheme I) follow procedures disclosed in earlier reports.[7,8] The urea linkage present in **7** was installed as previously reported according to method A. Elaboration of **Ia** or **Ib** at the N^1-position was carried out employing standard amide alkylating conditions. The conversion of the N^1-alkyl and protected 3-amino groups in **IIIa** to give **8** was then accomplished using methods B and A. The yields obtained for a number of the cited transformations were curiously substrate dependent and the sequence with which the reactions were carried out played a significant role in their successful execution. For this reason, the N^1-substituent of the initial alkylation product **IIIa** was occasionally elaborated according to method C (Scheme II) prior to removal of the C-3 amino protecting group. For the preparation of compounds like **40–42** (Scheme III), the N^1-substituent was transformed to the final product following skeletal assembly of the parent compound **V**. Representative reaction conditions are provided in the Experimental Section describing the preparation of compounds represented in these schemes.

For the synthesis of compounds **26** and **27**, both enantiomers of the requisite intermediate **VIIa** and **VIIb** were obtained in chirally homogeneous form according to the procedure summarized in Scheme IV. The key steps in the success of this operation were the emplacement of the chiral auxiliary in **VIa** and **VIb** via the intermediacy of an acylimidazole, separation of the resulting mixture of diastereomers by chromatography and crystallization, and then alkylation of the N^1-position without detectable racemization at C-3 to yield **VIIa** and **VIIb**. The carbamate side chain which served the 2-fold purpose of chiral auxiliary and amino protecting group was then cleaved using conventional methods. Interestingly, the carbamates **VIIa** and **VIIb** showed different chemical reactivities as the conditions employed in the removal of the carbamate side chain in **VIIa** were ineffective in the

† This paper is dedicated with fondness and respect to the memory of our dear colleague and beloved friend, Dr. Tah-jyh Lee.

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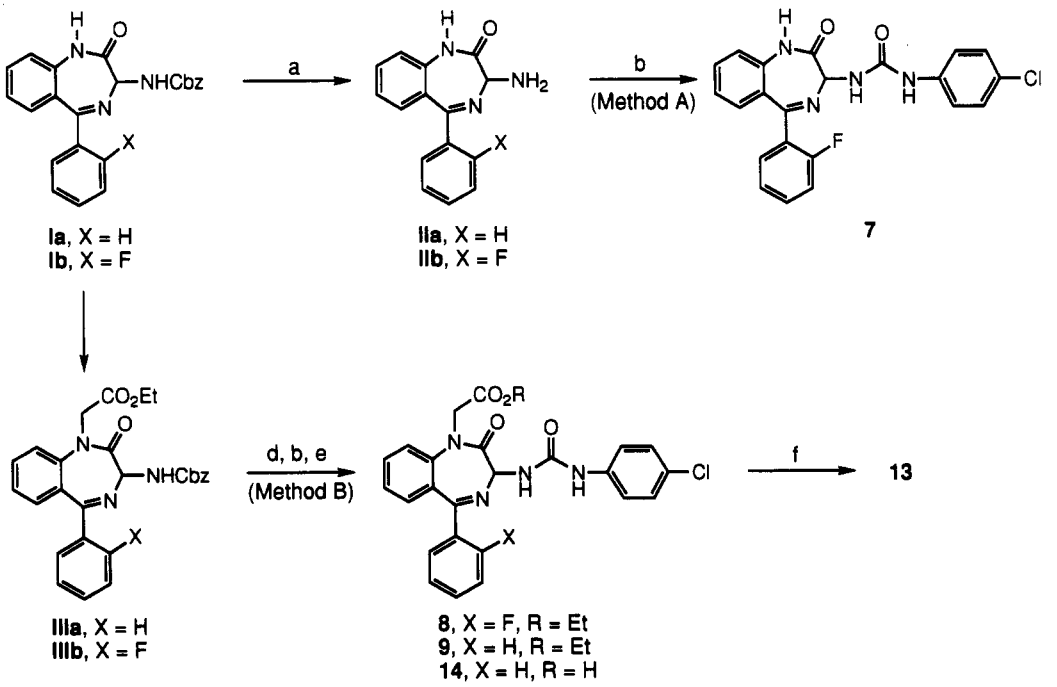
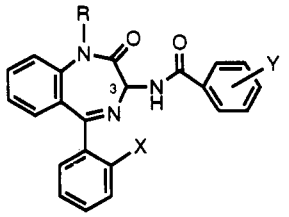
Scheme I[a]



[a] Reagents and conditions: (a) refs 7, 8; (b) *p*-chlorophenyl isocyanate, THF, 23 °C, 12 h; (c) NaH, DMF, $BrCH_2CO_2Et$, 0–23 °C, 3 h; (d) 90% HCO_2H, CH_3OH, Pd/C, 23 °C, 4 h; 10% Na_2CO_3; (e) 1 N NaOH, THF, 23 °C, 8 h; (f) benzyl alcohol, DCC, CH_2Cl_2, 23 °C, 48 h.

Table I. Inhibition of Binding of [^{125}I]CCK-8 to Guinea Pig Brain CCK Receptors and to Rat Pancreatic Receptors by 3-(Benzoylamino)-1,4-benzodiazepines



					IC_{50} (μM)[a]		
no.	X	Y	R	3-stereo	CCK-B	CCK-A	selectivity B/A
3	F	4-Cl	CH_2CO_2Et	*RS*	1.9	0.11	0.06
4	F	2-Cl	CH_2CO_2Et	*RS*	3.2	>30	>9
5	H	4-CF_3	CH_3	*S*	4.6	1.3	0.3
6	H	4-CF_3	CH_3	*R*	3.3	115	35

[a] Receptor binding is expressed as IC_{50}, the concentration of compound required for half-maximal inhibition of the binding of [^{125}I]CCK-8 to CCK-B receptors in guinea pig cerebral cortex and to CCK-A receptors in rat pancreatic tissue. Values were obtained from one or two separate experiments.

deblockade of **VIIb**. The corresponding amino enantiomers derived from **VIIa** and **VIIb** were subsequently reacted with 4-chlorophenyl isocyanate to afford **26** and **27**, respectively.

The compounds listed in Table III were made available by procedures outlined in Scheme V.[7-10] Usually the amine **VIII** could be transformed to an arylurea according to method A. In certain instances it proved expedient to prepare the reactive carbamate **IX** and to convert the latter material to a benzodiazepine urea (e.g. **83**) using method D. Alternatively, the requisite intermediates for the generation of arylureas could be generated *in situ* according to method E (e.g. **88**).

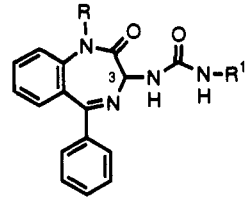
The pyridylbenzodiazepines recorded in Table IV were synthesized by adaptation of the route outlined in Scheme VI which exemplifies the preparation of compound **114**. The starting 2-(2-aminobenzoyl)pyridine was secured according to literature methods.[11] (The regioisomeric 3- and 4-(2-aminobenzoyl)pyridines employed for the synthesis of **112** and **113** were similarly prepared;[11,12] the requisite (aminobenzoyl)pyridines needed for the synthesis of compounds **108–110** were also obtainable according to published procedures.[13-15] 2-(2-Aminobenzoyl)pyridine was reacted with the mixed anhydride derived from isobutyl chloroformate and α-[(*tert*-butyloxycarbonyl)-amino]-N^{α}-(benzyloxycarbonyl)glycine[16] to yield **X**. Removal of the *tert*-butyloxycarbonyl protecting group with gaseous HCl afforded the desired α-aminoglycinamide intermediate; the latter compound was immediately subjected to conditions leading to the cyclized product **XI**. To complete the synthesis, the *N*,*N*-diethylacetamide substituent was installed at the N^1-position under standard conditions giving **XII**, and the C-3 amino group was then elaborated to the desired arylurea **114** in the usual manner (method A).

Biology

The methods employed for the determination of [^{125}I]-CCK-8 binding to rat pancreas and guinea pig cortex, and [^{125}I]gastrin binding to guinea pig gastric glands were similar to those previously described.[17] For a select group of indicated compounds the radioreceptor binding protocol for rat pancreas and guinea pig cerebral cortex membranes was modified according to the procedure detailed in the Experimental Section.

For *in vivo* studies, gastrin-stimulated acid secretion was determined in mice using the previously reported modified method of Gosh and Schild.[17] Net agonist-stimulated acid secretion was determined from the acid outputs of animals pretreated concurrently with vehicle (0.5% methocel) or test compounds prior to and after agonist administration. Percent inhibition was determined by comparing the net agonist-stimulated acid output in control and treated groups. Test compounds were administered to separate groups of animals at various time intervals prior to pentagastrin treatment by the intraduodenal (id, 5, 20, and 45 min) or the oral (po, 90 and 180 min) routes.

Table II. Inhibition of Binding of [^{125}I]CCK-8 to Guinea Pig Brain CCK Receptors and to Rat Pancreatic Receptors by 1,4-Benzodiazepines Bearing Functionalized N^1-Substituents



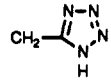
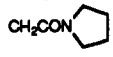
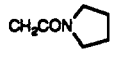
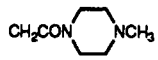
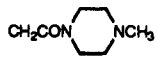
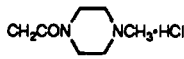
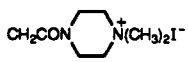
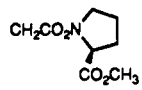
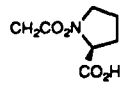
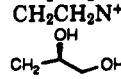
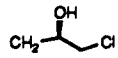
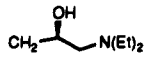
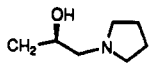
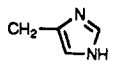
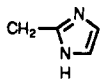
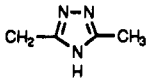
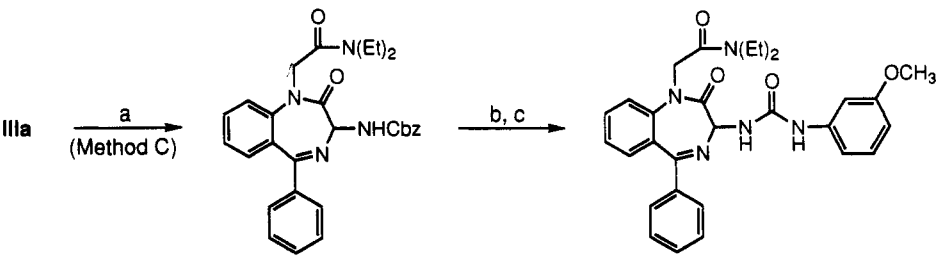
no.	R	R^1	3-stereo	IC$_{50}$ (μM)[a] CCK-B	CCK-A	selectivity B/A
7[b]	H	4-chlorophenyl	*RS*	0.27	0.11	0.4
8[b]	CH_2CO_2Et	4-chlorophenyl	*RS*	0.0012	0.22	183
9	CH_2CO_2Et	4-chlorophenyl	*RS*	0.001	0.37	370
10	$CH_2CH_2CO_2Et$	4-chlorophenyl	*RS*	0.0059	0.49	204
11	$CH_2CH_2CO_2Et$	3-methoxyphenyl	*RS*	0.001	0.34	340
12	CH_2CO_2Et	(*S*)-α-methylbenzyl	*RS*	>0.1	4.8	<48
13	CH_2CO_2Bn	4-chlorophenyl	*RS*	0.044	1.3	30
14	CH_2CO_2H	4-chlorophenyl	*RS*	0.072	0.056	0.77
15	CH_2CO_2H	3-methylphenyl	*RS*	0.38[c]	0.0076[c]	0.02
16	$CH_2CH_2CO_2H$	3-methoxyphenyl	*RS*	0.25	0.009	0.036
17		4-chlorophenyl	*RS*	0.49	2.1	4
18	$CH_2CONHEt$	4-chlorophenyl	*RS*	0.011	2.1	191
19	$CH_2CONHBn$	4-chlorophenyl	*RS*	0.102	2.4	24
20	CH_2CONEt_2	4-chlorophenyl	*RS*	0.0006	0.4	667
21	$CH(CH_3)CONEt_2$	4-chlorophenyl	*RS*	0.022	0.41	19
22	CH_2CONEt_2	2-chlorophenyl	*RS*	0.0038	0.2	53
23	CH_2CONEt_2	3-methoxyphenyl	*RS*	0.00022	0.12	545
24		3-methoxyphenyl	*RS*	0.00024	0.17	708
25		4-chlorophenyl	*RS*	0.0016[c]	1.0[c]	625
26		4-chlorophenyl	*S*	0.013[c]	2.5[c]	192
27		4-chlorophenyl	*R*	0.0014[c]	0.9[c]	643
28		4-chlorophenyl	*RS*	0.0008	1.2	1,500
29		3-methoxyphenyl	*RS*	0.0044	1.4	318
30		3-methylphenyl	*RS*	0.0035	0.76	217
31		3-methylphenyl	*RS*	0.058	6.2	107
32		3-methylphenyl	*RS*	0.048	1.1	23
33		4-methylphenyl	*RS*	0.19	4	21
34		3-methoxyphenyl	*RS*	0.0097	1.4	144
35		3-methylphenyl	*RS*	0.130	20	15
36	CH_2CH_2OH	3-methylphenyl	*RS*	0.044[c]	0.27[c]	6
37	$CH_2CH_2NMe_2$	3-methylphenyl	*RS*	0.026[c]	1.89[c]	73
38	$CH_2CH_2NMe_2$	3-methoxyphenyl	*RS*	0.192[c]	3.09[c]	16
39	$CH_2CH_2N^+Me_3I^-$	3-methoxyphenyl	*RS*	1.1	17	15
40		4-chlorophenyl	*RS*	0.104[c]	>9% at 3[c,d]	>30
41		4-chlorophenyl	*RS*	0.006[c]	>15% at 3[c,d]	>500
42		4-chlorophenyl	*RS*	0.41[c]	>14% at 3[c,d]	>7

Table II. (Continued)

no.	R	R^1	3-stereo	IC_{50} (μM)[a] CCK-B	CCK-A	selectivity B/A
43		4-chlorophenyl	*RS*	0.3[c]	>16% at 3[c,d]	>10
44		3-methylphenyl	*RS*	0.0079[c]	0.011[c]	1
45		3-methylphenyl	*RS*	0.059[c]	0.258[c]	4
46		3-methylphenyl	*RS*	0.0097[c]	0.566[c]	58
47	$CH_2CH_2OCOCH_2NEt_2$	3-methylphenyl	*RS*	0.0056	0.19	34
48	$(CH_2)_2OCO(CH_2)_2CO_2H$	3-methylphenyl	*RS*	0.0072	0.037	5

[a] Binding affinities as defined in Table I, footnote. Values were obtained from one to four separate experiments. [b] 5-(2-Fluorophenyl) analog. [c] Modified binding assay protocol; see the Experimental Section. [d] Percent inhibition.

Scheme II[a]



[a] Reagents and conditions: (a) 1 N NaOH, THF, 23 °C, 3–8 h; $SOCl_2$, toluene, 90 °C, 1 h; diethylamine, THF, 23 °C, 1 h; (b) 90% HCO_2H, CH_3OH, Pd/C, 23 °C, 4 h; (c) *m*-methoxyphenyl isocyanate, NEt_3, THF, 23 °C, 1h.

The oral bioavailability in rats of a select number of benzodiazepine CCK-B antagonists was established by an HPLC method as described in the Experimental Section.

Results and Discussion

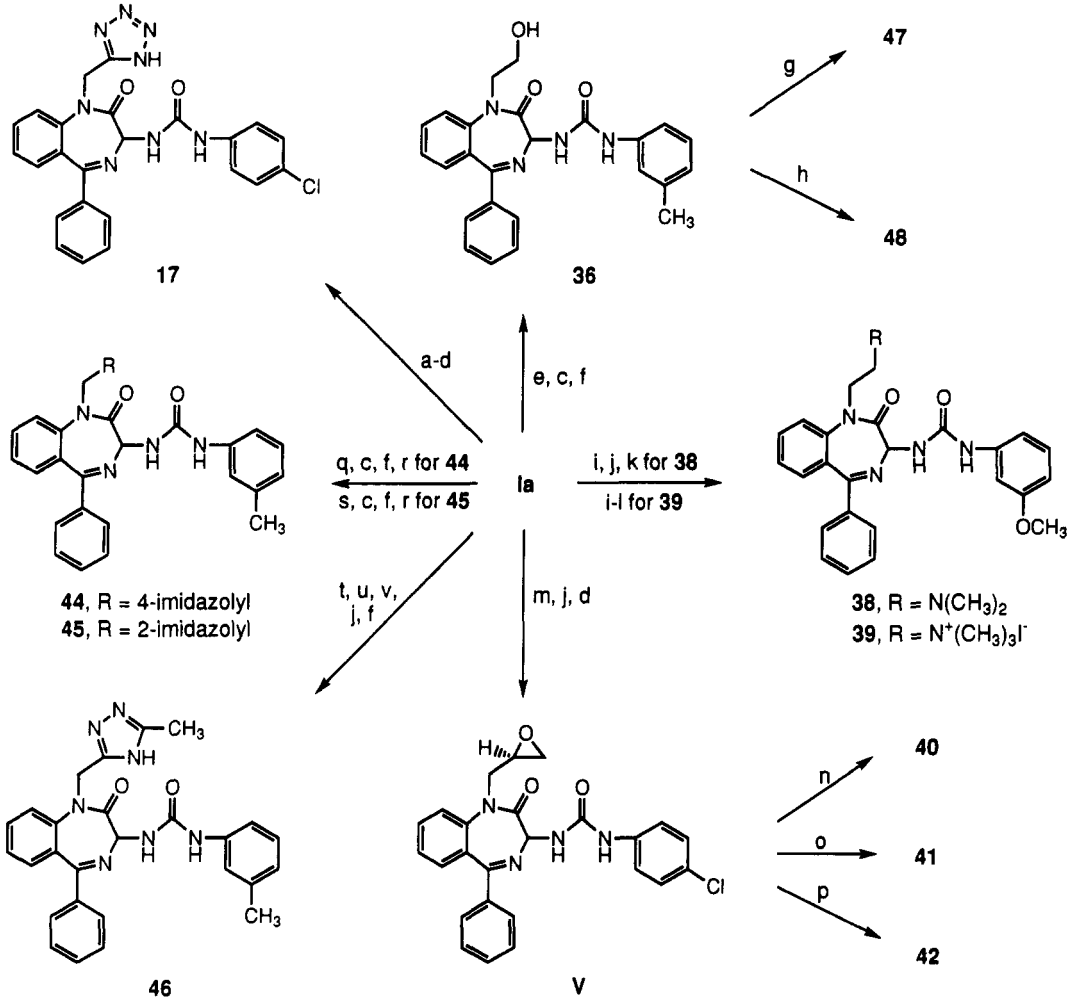
In the early 1980s, radioligand binding studies produced evidence that distinct CCK receptors exist in peripheral and central tissues.[1,18] These findings were further confirmed with the development of the CCK-A antagonist MK-329 (1, devazepide, formerly L-364,718) with which it was unequivocally demonstrated that CCK-A and CCK-B receptors are distinguishable entities.[3,4,19,20] Having discovered highly potent CCK-A selective antagonists, we redirected our efforts toward CCK-B selective agents to aid in further elucidating the physiological significance of CCK.

In advance of a committed research program, indications that selectivity in the reverse sense could be attained (i.e. for CCK-B over CCK-A receptors) were provided by the compounds **3–6** listed in Table I. For example, the straightforward repositioning of a chlorine atom on the phenyl ring in the CCK-A-selective **3** is a sufficient structural perturbation to decrease affinity for this receptor subtype more than 100-fold as in compound **4**. While the subtle electronic and steric effects of this transposition on the CCK-A receptor binding affinity are manifest, CCK-B receptor affinity remains virtually unaffected. Along similar lines, a 2-order of magnitude change in CCK-A receptor affinity was realized by inverting the stereocenter in **5** to yield **6**. As with analogue **4**, the CCK-B receptor affinity of **6** remained essentially unchanged. Although the potencies of compounds **4** and **6** are only in the micromolar range, the net result of the above-mentioned structural changes to **3** and **5** is a reversal of selectivity in favor of the CCK-B receptors. These observations provided a major impetus for the ensuing CCK-B antagonist discovery program.

On the basis of the enhanced receptor binding potency of the 3-carboxamido-1,4-benzodiazepines,[21] vis-à-vis the 3-alkyl series,[22] we incorporated an additional nitrogen atom in the side chain of CCK-A antagonists such as **3**, thereby connecting an aryl ring and the 1,4-benzodiazepine core with a urea linkage. The first compound derived from this modest structural amendment was the prototype, compound **7**.[23] As the results in Table II indicate, compound **7** was essentially equipotent with **3** in binding to the CCK-A receptors and displayed an approximate 6-fold increase in affinity for the CCK-B receptors. Substituting the N^1-position of **7** with a carbethoxymethyl group produced the potent CCK-B-selective compound **8**, which demonstrated the potential of our approach. Thus, the seemingly innocuous change of replacing the 3-arylcarboxamido group in **3** with an arylurea side chain was sufficient to skew its CCK receptor selectivity profile in the desired manner. It can be noted that the 3-urea linkage is one element common to all CCK-B-selective compounds described in this report, and it is of some pedagogical interest that other CCK antagonists have been discovered, though not necessarily of the 1,4-benzodiazepine structural class, which also contain a urea moiety;[24–29] some of these compounds display excellent CCK-B potency and selectivity.[25–27,29]

The success of compound **8** and its desfluoro analog **9** prompted us to undertake extensive structure/activity studies, the key findings from which may be illustrated by using the analogues listed in Tables II–IV. While compounds **8** and **9** were derived precisely in the chronological sequence indicated, the select list of remaining analogues

Scheme III[a]



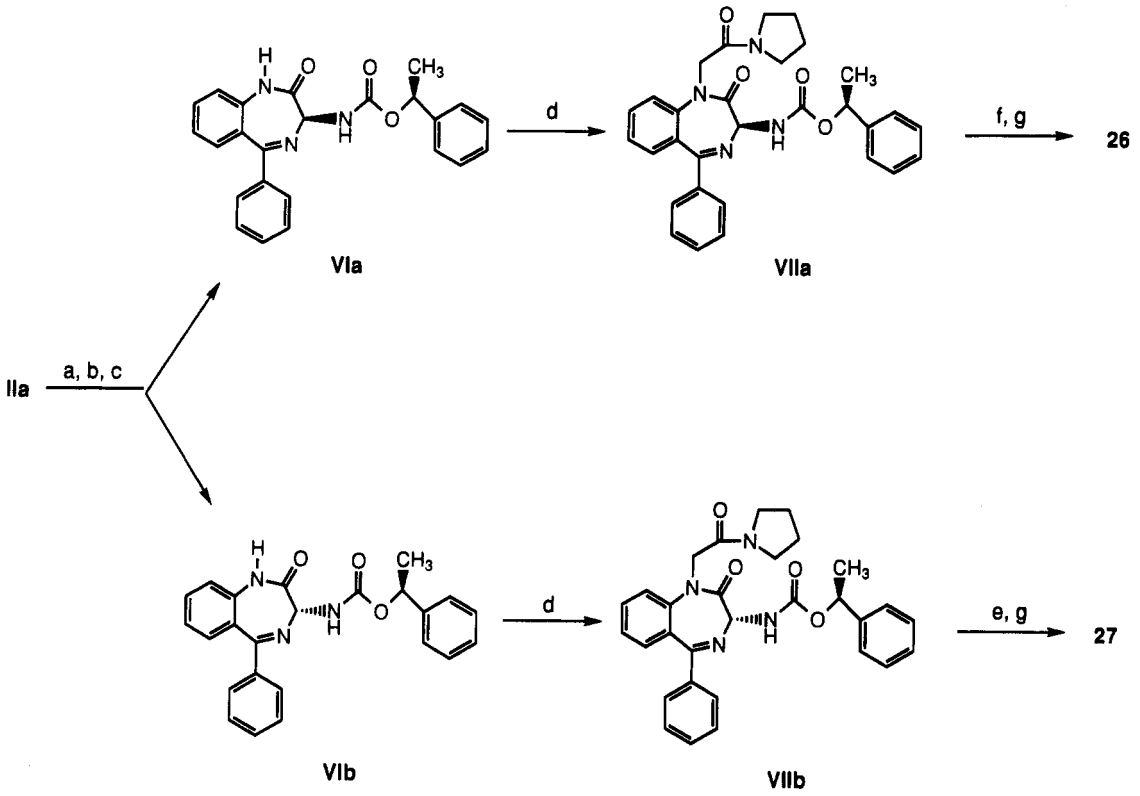
[a] Reagents and conditions: (a) NaH, DMF, $ClCH_2CN$, 0 °C, 2 h; (b) NaN_3, NH_4Cl, DMF, 110 °C, 4 h; (c) HBr(g), CH_2Cl_2, 0–23 °C, 1 h; (d) *p*-chlorophenyl isocyanate, NEt_3, THF; (e) NaH, DMF, ethylene oxide, 100 °C, 3 h; (f) *m*-tolyl isocyanate, NEt_3, THF, 23 °C; (g) *N,N*-diethylglycine, EDC, HBT, NEt_3, DMF, 23 °C; (h) succinic anhydride, 4-DMAP, CH_2Cl_2, 12 h; (i) NaH, DMF, 2-(dimethylamino)ethyl chloride, 0–23 °C, 72 h; (j) HCO_2H, MeOH, Pd/C, 23 °C 1.5 h; (k) *m*-methoxyphenyl isocyanate, THF, 1 h; (l) MeI, acetone, 57 °C, 2 h; (m) NaH, DMF, (2*S*)- (+)-glycidyl 3-nitrobenzenesulfonate, 0–23 °C, 72 h; (n) HOAc, H_2O, 23 °C, 18 h; (o) pyridine, hydroxylamine hydrochloride, 23 °C, 60 h; (p) dimethylamine, THF, 0–23 °C, 60 h; (q) NaH, DMF, 1-(2,4-dinitrophenyl)-4-(chloromethyl)imidazole, 0–23 °C, 2 h; (r) thiophenol, DMF, 23 °C, 1 h; (s) NaH, DMF, 1-(2,4-dinitrophenyl)-2-(chloromethyl)imidazole, 0–23 °C, 1 h; (t) chloroacetamide, $CsCO_3$, DMF, 0–23 °C, 2 h; (u) *N,N*-dimethylacetamide dimethyl acetal, 100 °C, 3 h; (v) hydrazine, HOAc, 90 °C, 3 h.

shown in Tables II and III were developed in approximately parallel fashion and are segregated only for the purpose of clarity. Implicit in the discussion which follows is the fact that arylurea functional group changes which resulted in CCK-B potency and selectivity improvements for the compounds collated in Table III were incorporated, when feasible, into the series depicted in Table II. Underlying the structural diversity of those compounds were the objectives of developing an agent which would satisfy the criteria of high CCK-B receptor affinity and selectivity, acceptable aqueous solubility, oral activity, and long duration of action *in vivo*.

The focus of our investigation at the incipient stages was to optimize the pharmacological properties of compounds 8 and 9. As the data for structures 10–13 in Table II indicate, homologation of the N^1-ester group had minimal effect on receptor binding potency although the consequences of extending the urea linker, as in 12, were pronounced. Disconcerting, however, was the finding that 8 was not orally active. Functional studies determining whether 8 acts as an agonist or antagonist of brain CCK-B receptors were not undertaken. Nevertheless, since all of the compounds of this paper have comparable affinity for brain CCK-B and gastrin receptors, the effect of intravenous and oral administration of 8 on pentagastrin-stimulated acid secretion from the *in situ* perfused mouse stomach was examined.[30-32] When 8 was administered intravenously at the ED_{50} dose (0.7 mg/kg) 5 min prior to pentagastrin, it effectively antagonized pentagastrin-stimulated acid secretion in a concentration dependent manner. Compound 8 was less effective (ED_{50} > 2.0 mg/kg) as an antagonist of pentagastrin when it was administered intravenously 60–80 min prior to the agonist challenge, suggesting a short duration of action by this route of administration. When administered orally 85–100 min prior to pentagastrin, 8 was ineffective (ED_{50} > 6 mg/kg) as an antagonist of pentagastrin-stimulated acid secretion. The data show an iv/po ratio of >9 indicating that 8 is poorly bioavailable in the mouse following oral administration. Previous studies with MK-329 had shown good oral bioavailability in this species.[4]

We reasoned that the N^1-ester group in 8 is a chief liability, a locus exposed to attack by esterases, perhaps accounting for the short duration of action of 8 and even for its lack of oral activity. The modification of the N^1-position was therefore examined in some detail. The N^1-position was substituted with acidic, neutral, and basic functionality. Although the carboxylic acid moieties and

Scheme IV [a]



[a] Reagents and conditions: (a) carbonyldiimidazole, THF, 23 °C, 12 h; (b) (*S*)-(−)-*sec*-phenethyl alcohol, THF, 67 °C, 75 h; (c) SiO_2 chromatography; (d) NaH, DMF, *N*-(2-iodoacetyl)pyrrolidine, 0 °C, 2 h; (e) 90% HCO_2H, CH_3OH, Pd/C, 23 °C; 10% Na_2CO_3; (f) HBr(g), CH_2Cl_2, 0 °C, 1 h; 10% Na_2CO_3; (g) *p*-chlorophenyl isocyanate, NEt_3, THF, 23 °C, 1 h.

the corresponding bioisosteric tetrazole ring impart a modicum of aqueous solubility in compounds **14–17**, these changes were detrimental to CCK-B receptor binding affinity. Substantially greater affinities for the CCK-B receptors were achieved by replacing the N^1-substituent in **8** with amides, specifically tertiary carboxamides. The results indicate that, compared with the breakthrough compound **8**, the amides **20**, **23**, **24**, and **28** have greater affinities for the CCK-B receptors as well as improved selectivities versus the CCK-A receptors. The added steric bulk at the N^1-position of the latter compounds is therefore well tolerated and likely interacts with a lipophilic site on the CCK-B receptors. Moreover, tertiary amides, like esters **8–11**, may also play a hydrogen bond accepting role in binding to the receptors; by contrast, compounds **14–19**, perhaps by virtue of their acidity and/or hydrogen bond donating properties (*vide infra*) do not bind as well.

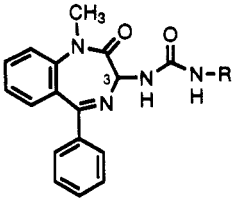
In spite of their excellent CCK-B receptor affinities and selectivities, functional analysis of compounds **20–25** in the *in situ* perfused mouse stomach preparation indicated that they were ineffective in antagonizing pentagastrin when administered orally. Since these compounds proved to be virtually insoluble in aqueous media (<5 μg/mL, pH 7.4), we considered the possibility that the physical properties of these analogues may be one of the factors unduly influencing their *in vivo* behavior. For this reason the derivatives **28–46** were prepared.

It was disappointing to discover that the addition of a basic nitrogen atom to the pyrrolidine ring of **24** and **25** yielding **29** and **28**, respectively, has remarkably little influence on the aqueous solubility properties of the latter derivatives (<10 μg/mL, pH 5.2). Similar results were obtained with compounds **30–33**; the best of the group, **30**, was soluble only to the extent of 19 μg/mL at pH 7.4. The proline-derived analogue **35** was marginally more soluble than the basic series above but it had unacceptably low receptor binding affinity.

Though devoid of the N^1-acetamido carbonyl group of the foregoing analogues, compounds **36–46** do contain polar binding components. We hoped that these groups would render compounds **36–46** slightly more water soluble. Further, we hypothesized that the N^1-substituents of the latter compounds would interact with approximately the same binding determinants on the CCK-B receptors as the N^1-acetamido-containing analogues and therefore retain their potency. In practice, the anticipated increase in aqueous solubility was not realized (<10 μg/mL, pH 7.4 for all compounds). Inspection of the binding data in Table II shows, excepting compounds **41** and **44**, that the N^1-modifications exemplified by compounds **36–46** are detrimental to CCK-B receptor affinity. Even though the N^1-structural changes which transform **20** and **25** into **42** and **43**, respectively, appear minor, the effect of these changes on CCK-B binding affinity is striking. A similar result obtains for the related pair of analogues **23** and **38**.

It is important to note that the most potent and selective CCK-B receptor ligands listed in Table II are racemic mixtures. As the lead prototype compounds **5** and **6**, each a single enantiomer, exhibited a binding preference between CCK receptor subtypes, it was imperative to explore whether this dichotomy in selectivity could be duplicated with one of the more potent analogues in Table II. Chemical resolution of **25** afforded the corresponding *S* and *R* enantiomers **26** and **27**, respectively. Their analysis yielded the unanticipated result that both isomers display selectivity in binding for the CCK-B receptor subtype. In accord with the selectivity of the *R* enantiomer **6** for the CCK-B receptor, compound **27** shows a similar preference over its enantiomeric counterpart **26**. However,

Table III. Inhibition of Binding of [^{125}I]CCK-8 to Guinea Pig Brain CCK Receptors and to Rat Pancreatic Receptors by N^1-Methyl-1,4-Benzodiazepines



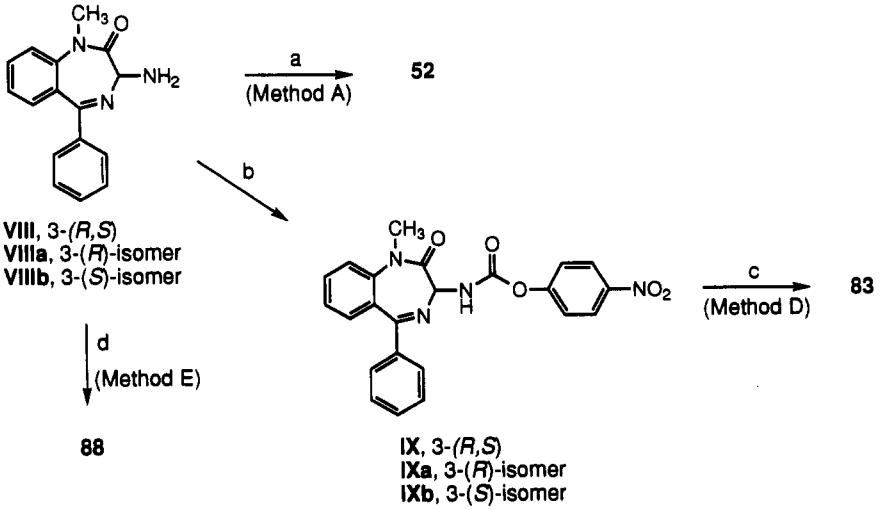
no.	R	3-stereo	IC_{50} (μM)[a] CCK-B	IC_{50} (μM)[a] CCK-A	selectivity B/A
49[b]	hydrogen	*RS*	>100	55	>0.5
50	*tert*-butyl	*RS*	38	6.8	0.2
51	cyclohexyl	*RS*	3.0	2.4	0.8
52	phenyl	*RS*	0.032	0.0083	0.26
53	benzyl	*RS*	0.86	0.49	0.6
54	α-methylbenzyl[c]	*RS*	11	0.43	0.04
55	4-chlorophenyl	*RS*	0.0813[d]	1.2[d]	15
56	4-chlorophenyl	*S*	1.1[d]	0.11[d]	0.1
57	4-chlorophenyl	*R*	0.0196[d]	2.2[d]	112
58	3-chlorophenyl	*RS*	0.0098	0.0082	1
59	3-chlorophenyl	*R*	0.0075	0.29	39
60	2-chlorophenyl	*S*	0.28	0.00026	<0.01
61	2-chlorophenyl	*R*	0.061	0.41	6.7
62	2,4-dichlorophenyl	*RS*	0.22	0.003	0.01
63	3,4-dichlorophenyl	*RS*	0.067	0.026	0.4
64	4-fluorophenyl	*RS*	0.066	0.046	0.7
65	3-fluorophenyl	*RS*	0.054	0.010	0.2
66	3-bromophenyl	*RS*	0.005	0.0044	1
67	4-bromophenyl	*RS*	0.048	0.13	2.7
68	3-bromophenyl	*R*	0.0038	0.84	221
69	3-iodophenyl	*R*	0.0069[d]	0.8[d]	116
70	4-nitrophenyl	*RS*	0.046	0.21	4.5
71	3-nitrophenyl	*RS*	0.011	0.034	3
72	2-nitrophenyl	*RS*	1.2	0.003	<0.01
73	4-methoxyphenyl	*RS*	0.026	0.165	6
74	3-methoxyphenyl	*RS*	0.003	0.0062	2
75	3,5-dimethoxyphenyl	*RS*	2.3	0.31	0.1
76	3-methoxyphenyl	*S*	0.3	0.0013	<0.01
77	3-methoxyphenyl	*R*	0.0022	0.60	272
78	2-methoxyphenyl	*RS*	1.2	0.6	0.5
79	4-methylphenyl	*RS*	0.006	0.057	9.5
80	4-methylphenyl	*R*	0.0065	3.1	477
81	3-methylphenyl	*S*	0.28[d]	0.0047[d]	0.01
2	3-methylphenyl	*R*	0.0085[d]	0.74[d]	87
82	3-methylphenyl[e]	*R*	0.04[d]	3.8[d]	95
83	3,4-dimethylphenyl	*R*	0.022[d]	0.31[d]	14
84	3,5-dimethylphenyl	*R*	0.267[d]	0.72[d]	2.7
85	4-(trifluoromethyl)phenyl	*R*	0.0057	1.3	228
86	3-(trifluoromethyl)phenyl	*R*	0.0038	0.74	195
87	5-indanyl	*R*	0.0027[d]	0.9[d]	333
88	3-styrenyl	*R*	0.035[d]	1.67[d]	48
89	3-acetylenylphenyl	*R*	0.022[d]	0.402[d]	18
90	3-biphenylyl	*RS*	0.112[d]	0.123[d]	1
91	3-hydroxymethylphenyl	*R*	0.019	0.021	1
92	3-(1-hydroxy-1-methylethyl)phenyl	*R*	0.0059[d]	0.406[d]	69
93	3-acetylphenyl	*R*	0.0048[d]	1.3[d]	361
94	3-hydroxyphenyl	*R*	0.0147[d]	0.060[d]	1
95	3-acetoxyphenyl	*R*	0.5	6.6	13
96	3-aminophenyl	*R*	0.033	4.33	131
97	3-*t*-butyloxycarbonylaminomethylphenyl	*R*	0.17	0.20	1
98	3-phenylaminophenyl	*RS*	>3 at 22%	2.56[d]	-
99	3-aminomethylphenyl	*R*	0.719[d]	0.16[d]	0.22
100	3-cyanophenyl	*R*	0.027[d]	3.1[d]	115
101	4-carboxyphenyl	*RS*	>0.1	>10	-
102	3-carboxyphenyl	*RS*	0.0097[d]	0.014[d]	1.4
103	3-carbomethoxyphenyl	*R*	0.008[d]	1.2[d]	150
104	3-(carbomethoxymethyl)phenyl	*R*	0.0326[d]	2.1[d]	64
105	3-(carboxymethyl)phenyl	*R*	0.0049[d]	0.061[d]	12
106	1-naphthyl	*RS*	0.079	0.068	0.9
107	3,4-(methylenedioxy)phenyl	*R*	0.026[d]	>3 at 20%[d]	>100

[a] Binding affinities as defined in Table I, footnote. Values were obtained from one to four separate experiments. [b] 5-(2-Fluorophenyl) analog. [c] (*S*)-Configuration. [d] Modified binding assay protocol; see the Experimental Section. [e] N-1 desmethyl derivative.

if the chiralities of compounds **5** and **6** are a guide, it appears the influence of the N^1-pyrrolidinylacetamide group in **26** overrides the impact of the stereochemical disposition of the (4-chlorophenyl)urea side chain on CCK-B receptor affinity.

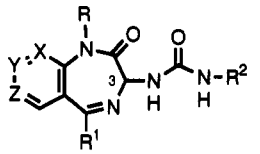
The temptation to identify trends which correlate

Scheme V[a]



[a] Reagents and conditions: (a) phenyl isocyanate, THF, 23 °C, 1 h; (b) *p*-nitrophenyl chloroformate, NEt_3, THF, 0 °C, 1 h; (c) 3,4-dimethylaniline, NEt_3, DMF, 23 °C, 2 h; (d) 3-aminostyrene, triphosgene, NEt_3, THF, 0–23 °C, 1 h.

Table IV. Inhibition of Binding of [^{125}I]CCK-8 to Guinea Pig Brain CCK Receptors and to Rat Pancreatic Receptors by Heteroaryl 1,4-Benzodiazepines



								IC$_{50}$ (μM)[a]		
no.	X	Y	Z	R	R^1	R^2	3-stereo	CCK-B	CCK-A	selectivity B/A
108	N	C	C	methyl	phenyl	3-methylphenyl	*RS*	7% at >3[b,c]	0.104[c]	<0.01
109	C	N	C	methyl	phenyl	3-methylphenyl	*RS*	19% at >3[b,c]	0.144[c]	<0.01
110	C	C	N	methyl	phenyl	3-methylphenyl	*RS*	0.632[c]	0.0614[c]	0.1
111	C	C	C	methyl	2-pyridyl	3-methylphenyl	*RS*	0.066	0.065	1
112	C	C	C	methyl	3-pyridyl	3-methylphenyl	*RS*	0.092	2.3	25
113	C	C	C	methyl	4-pyridyl	3-methylphenyl	*RS*	0.052	0.39	7.5
114	C	C	C	diethylacetamido	2-pyridyl	3-methylphenyl	*RS*	0.00056[c]	0.435[c]	776
115	C	C	C	methyl	phenyl	4-pyridyl	*RS*	1.07[c]	1.51[c]	1.4
116	C	C	C	methyl	phenyl	3-pyridyl	*RS*	0.31[c]	0.12[c]	0.4
117	C	C	C	methyl	phenyl	2-pyridyl	*RS*	0.337[c]	0.447[c]	1.3
118	C	C	C	methyl	phenyl	3-(6-aminopyridyl)	*R*	0.5	3.0	6
119	C	C	C	methyl	phenyl	3-(6-methoxypyridyl)	*R*	0.46[c]	2.9[c]	6.3
120	C	C	C	methyl	phenyl	3-(6-chloropyridyl)	*R*	0.046[c]	23% at 3[b,c]	>65
121	C	C	C	methyl	phenyl	2-quinolinyl	*RS*	0.026	0.18	7
122	C	C	C	methyl	phenyl	6-quinolinyl	*RS*	0.052	0.31	6

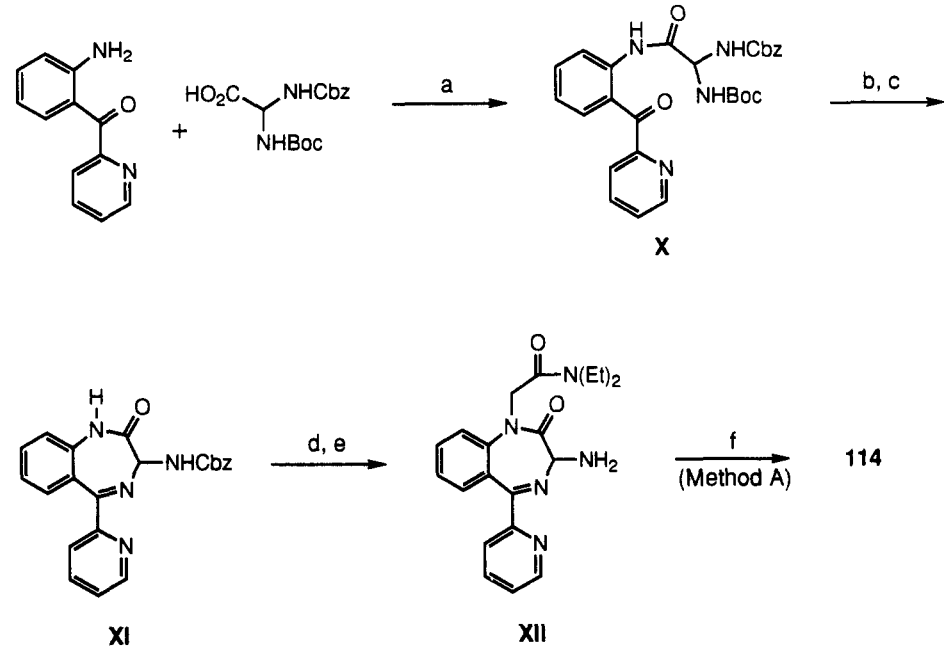
[a] Binding affinities as defined in Table I, footnote. Values were obtained from one to four separate experiments. [b] Percent inhibition. [c] Modified binding assay protocol; see the Experimental Section.

CCK-B binding affinity with the aforementioned N^1-structure modifications is mitigated by seeming inconsistencies in the receptor binding data. For example, on the basis of the acidic compounds **14** and **15**, the secondary amide **18**, and the *N*^{1}-alkyl alcohols **40**, **42**, and **43**, one might conclude that polar, hydrogen bond donating groups are responsible for decreasing receptor binding affinity. The potency and selectivity of **41** stands in contradiction. The succinoyl derivative **48** too, in contrast with N^1-carboxylic acid analogues **14** and **15**, displays respectable CCK-B receptor affinity. Above all, these results illustrate the high levels of precision required to adjust receptor affinity using chemical structure variations.[21,33] If the N^1-position is appropriately customized, such changes can lead to potent and selective CCK-B receptor ligands. However, the high sensitivity of CCK-B receptor to small structural variations, as for example those compounds listed in Table II, makes the optimization of receptor ligands in a predictive manner an imposing task.

For the series of compounds collated in Table III the N^1-substituent was held constant as methyl. The corresponding desmethyl derivatives were prepared for a select number of analogues in Table III, and these were uniformly less potent CCK receptor ligands (data not shown). As is evident from the binding data for compounds **49–54**, an arylurea side chain is preferrable to an unsubstituted or alkylurea side chain. Further, on the basis of the derivatives **52**, **53**, and **54** it appeared to us that receptor affinity and sensitivity to arylurea modification was pronounced. Subsequent alterations were thus centered around various substituents and substitution patterns on the aromatic ring of the urea in **52**.

An assortment of functional groups was examined. These were chosen to modify the physical properties of **52** (e.g. solubility, partition coefficient) and to probe electronic and steric effects as they pertain to CCK-B receptor binding. Owing to the complimentarity of the N^1-substituent and the (4-chlorophenyl)urea side chain in **8** in achieving CCK-B receptor affinity and selectivity, the incorporation of a 4-chloro atom was also one of the first changes selected for **52**. The effect of this variation on CCK-B receptor binding was modest but the hoped for

Scheme VI[a]



[a] Reagents and conditions: (a) *i*-BuOCOCl, *N*-methylmorpholine, CH_2Cl_2, 0 °C, 15 min; 23 °C, 4 h; (b) HCl, EtOAc, 23 °C, 10 min; (c) NH_4OAc, HOAc, 23 °C, 12 h; (d) NaH, DMF, *N,N*-diethyliodoacetamide, 0–23 °C, 12 h; (e) HBr, CH_2Cl_2, HOAc, 23 °C, 1 h; 1 N NaOH; (f) *m*-tolyl isocyanate, THF, 23 °C, 15 min.

trend toward CCK-B selectivity is evident as the resulting compound **55** shows decreased CCK-A affinity. Other electron-withdrawing substituents in the 4-position were explored (fluoro, **64**; bromo, **67**; nitro, **70**; carboxy, **101**) with the result that no dramatic difference in CCK-B receptor affinity and selectivity versus analogue **55** was realized. The CCK receptor profile of the 4-methoxy (**73**) and 4-methyl (**79**) analogues are also comparable to the latter set of compounds. However, when **79** is compared directly with **55** it is evident that a small advance in CCK-B receptor binding potency has been achieved. Head to head comparison of **79** with the benchmark compound **8** shows that these two compounds bind to the CCK-B receptor subtype with virtually equal affinity. This observation led us to conclude that avid binding of 1,4-benzodiazepines to CCK-B receptors could be attained by alternative, though not necessarily interdependent, structural changes.

Results from earlier work (cf. Table I) indicated that the spatial orientation of the 3-position substituent on the 1,4-benzodiazepine ring can confer selectivity to these structure with regard to CCK-A and CCK-B receptor subtypes. This trend does not hold for the examples cited in Table II, compounds **26** and **27**. Though there is a difference in CCK-A and CCK-B receptor binding potency between these two enantiomeric compounds, the configurational change is not sufficient to completely reverse the sense of selectivity (i.e. both compounds are selective for the CCK-B receptor subtype). Perusal of the receptor binding data for the N^1-methyl series summarized in Table III shows that here the stereochemistry of the 3-position substituent has a more dramatic effect on CCK receptor subtype selectivity. While many analogues which are racemic foretell of no predilection for binding with either CCK receptor subtype, without exception, the preferred 3-position configuration for CCK-A receptor selectivity is *S*. Moreover, this is complemented with an exclusive preference for the CCK-B receptor by the corresponding 3*R*-configured isomer (cf. **56** vs **57**, **60** vs **61**, **76** vs **77**, **81** vs **2**). It can therefore be concluded that with the simple expedient of chemical resolution, N^1-methyl-3-(arylureido)-1,4-benzodiazepines, defined by structures such as **52**, can be tailored to bind either CCK-A or CCK-B receptor subtypes and by inference that this leads to a separation of physiological functions.

The receptor binding potency of the compounds listed in Table III can in some instances be amplified by appropriately substituting the phenyl ring of the 3-position urea side chain. Relatively few *ortho*-substituted analogues were examined (**60**, **61**, **72**, **78**); however, it seems reasonable to conclude that compared with the *meta* and *para* substituents, *ortho* groups are detrimental to CCK-B receptor affinity. Curiously, with regard to the *o*-chloro-substituted derivatives **60** and **61**, the former compound appears as an extremely potent CCK-A receptor ligand, rivaling the CCK-A receptor affinity of **1**, whereas the latter compound is an unremarkable CCK-B receptor ligand. The high CCK-A affinity and selectivity of **60** are of interest on two counts. First, *N*-(2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-2-chlorobenzamide, a close molecular relative of **60** and lacking only an NH in the 3-position side chain, is a mediocre (IC_{50} 1.7 μM) CCK-A receptor ligand.[21] The poor affinity of the latter compound has been attributed to electronic effects in the *o*-chlorobenzamide side chain. With the addition of an NH to the benzamide side chain, the *o*-chlorophenyl group in **60** is now in a slightly altered steric environment and the electronic effects appear to be mitigated by the urea linker. Secondly, though the urea linking unit is capable of modulating CCK receptor selectivity (cf. **4** vs **8**), as the high CCK-A affinity of **60** clearly indicates, it is not necessarily in favor of CCK-B selectivity. Clearly, aryl substitution is just as important as the nature of the C-3 linker for high and selective CCK-B receptor affinity.

While Table III is not all inclusive, for the cases we have studied there are marginal differences in CCK-B receptor affinity between *para*- and *meta*-substituted arylureas. One notable exception is the variance in potency between the 4- and 3-carboxyphenyl analogues **101** and **102**, respectively. On average, however, it seems fair to say that *meta*-substituted arylureas hold a slight potency

advantage when compared with the *para*-substituted counterparts (e.g. **58** vs **55**, **65** vs **64**, **66** vs **67**, **71** vs **70**, and **74** vs **73**). For this reason, greater emphasis was placed on fleshing out the SAR of these positional isomers. As is apparent from the data in Table III, a variety of functional groups including halo, alkyl, alkoxy, and carboxy are tolerated at the *meta* position. Amino and especially subtituted amino groups (e.g. **96**, **97**, **98**, and **99**) are conspicuously detrimental to CCK-B binding affinity.

The effect of disubstitution on the phenyl ring of the 3-urea side chain is also instructive. Although *meta* substitution may be slightly preferred to *para* substitution (vide supra), the addition of a second *meta* substituent to yield 3,5-disubstituted homologs is detrimental to receptor binding potency (cf. **75** vs **74** and **84** vs **2**). On the other hand, the addition of a second substituent to the *para* position, as in the case of **83**, is less harmful to binding affinity. Continuation with this 3,4-substitution pattern to also include annulated derivatives afforded **87**, one of the most potent CCK-B receptor ligands discovered in this series. However, in accord with the CCK-B receptor's sensitivity to structure at the phenylurea ring, the homologous methylenedioxy homolog **107** suffers a 1 order of magnitude loss in receptor binding affinity. In this regard, the receptor binding potency of the 1-naphthyl analog **106** is especially surprising considering its 2,3-disubstitution pattern (i.e. annulation of benzene on the phenylurea ring) and its racemic nature.

Only a limited number of compounds in Table III (e.g. **90**, **92**, **98**, and **106**) give a measure as to the ability of the CCK-B receptor to accommodate steric bulk in the phenylurea region of these benzodiazepines. In this context, however, the CCK-B binding potency of the biphenyl analog **90** is noteworthy considering that such bulky, lipophilic groups in analogous CCK-A receptor ligands (*para*-substituted benzamide groups) are detrimental to CCK-A binding affinity.[34] It appears, therefore, that the CCK-B receptor is less discriminating than the CCK-A receptor with respect to steric bulk and this may have implications regarding the nature of the site which binds the C^3-side chain in benzodiazepine CCK-B receptor ligands.[35]

During the course of this investigation, we also examined heteroaromatic rings that are topographically similar to the benzodiazepine phenylureas shown in Tables II and III but which might display different pharmacokinetic properties. In particular, the homologous series of pyridine analogs listed in Table IV was prepared. Among this collection of compounds, the diethylacetamido derivative **114**, is the most prominent member. Even as a racemate, its CCK-B receptor binding affinity and selectivity rivals that of the most potent compounds prepared. Yet, significant improvements in aqueous solubility and bioavailability relative to other potent compounds in Tables II and III were not realized.

Evaluation of the collection of analogs that were prepared in this investigation (Tables II–IV) led to the selection of compound **2** as the candidate for further study. Though a number of CCK-B receptor ligands were synthesized that display a singular advantage over compound **2**, e.g. receptor binding affinity or aqueous solubility, **2** invariably proved superior based on its overall physicochemical and pharmacological profile. As an illustration of this point, in Table V are indexed several analogs which are more potent, more water soluble, or based on their structure, might have been expected to be more resistant to metabolism than compound **2**. However, the consideration of additional criteria, oral bioavailability in the rat, and duration changes the overall perspective. The data in Table V indicate that the plasma levels determined for the text compounds after oral dosing were less than or equivalent to those for **2**. For compound **113**, the initial plasma level was higher than that for **2** but the plasma level at the second time point was much reduced. In the case of compound **111**, plasma levels were consistently higher than **2**; however, its CCK-B receptor binding potency is inferior to that of compound **2**.

Table V. Determination of Bioavailability of Selected Benzodiazepine Phenylureas in the Rat after Oral Dosing (2.5 mg/kg)

	plasma levels (μg/mL)			plasma levels (μg/mL)	
no.	30 min	120 min	no.	30 min	120 min
2	172	194	**86**	120	102
23	24	16	**111**	693	823
36	156	95	**112**	219	191
37	75	40	**113**	530	47
38	45	57	**114**	23	25
48	50	10			

Compound **2** (L-365,260) has been submitted for clinical development. A number of studies have been carried out which indicate promise for its potential utility.[33] In confirmation of animal studies, **2** has been shown to be a functional antagonist of both exogenous pentagastrin and CCK-4 elicited responses in humans.[6,36]

Summary

In our initial communication we issued a synopsis of the development of the selective CCK-B receptor antagonist **2** (L-365,260). In the present paper we detailed the derivation of **2** and several additional potent and selective companion CCK-B receptor ligands from progenitors which are potent CCK-A antagonists. Selectivity in binding to CCK-B receptors was achieved by altering the core 1,4-benzodiazepine CCK-A antagonist structures in at least five unique, though not necessarily interdependent, ways: (1) emplacement of a polar N^1-substituent, (2) changing the C-3 linking element from amide to urea, (3) inverting the stereochemistry of the 3-position side chain, (4) appropriately substituting the C-3 arylurea, and (5) identifying an optimum substitution pattern on C-3 arylurea. This work is a continuation of our efforts to customize the benzodiazepine core structure toward interacting with multiple receptor types with high affinity and specificity. Our present efforts to further refine the pharmacological profile of the CCK-B antagonists described herein will be disclosed in due course.

Experimental Section

Melting points were determined in open capillaries on either an Electrothermal or a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-300, Nicolet NT-360, or Varian VXR-400S spectrometer, each instrument with an internal lock on the deuterium resonance of the solvent. Data are reported as follows: chemical shift (multiplicity, integrated intensity). Mass spectra were obtained with a VG MM/ZAB-HF spectrometer. All compounds exhibited spectra consistent with their structure. HPLC was carried out on a Spectra Physics Model SP8800 liquid chromatograph using a Vydac C-18 column and a Pirkle covalent L-leucine reversible HPLC column. Elemental combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer. All final products prepared for biological studies were dried *in vacuo* over P_2O_5 at temperatures ranging from ambient to 110 °C, depending on the melting point of the sample and showed acceptable (±0.4%)

Table VI. Physical Data for Compounds of Tables II–IV

no.	formula	Scheme (method)	yield, %[a]	% purity HPLC	mp, °C (solvent[b])	analysis
2	$C_{24}H_{22}N_4O_2$	V (A)	64	99.9	208–210 (MeOH)	C,H,N
7	$C_{22}H_{16}ClFN_4O_2$	I (A)	86	99.5	278 (MeOH)	C,H,N
8	$C_{26}H_{22}ClFN_4O_4$	I (A)	98	98.7	253–254 (EtOAc)	C,H,N
9	$C_{26}H_{23}ClN_4O_4$	I (B)	76	96	228–229 (EtOAc)	C,H,N
10	$C_{27}H_{25}ClN_4O_4$	I (B)	79	99.1	251–253 (MeOH)	C,H,N
11	$C_{28}H_{28}H_4O_5$	I (B)	40	98.3	211–213 (Et_2O)	C,H,N
12	$C_{28}H_{27}FN_4O_4$	I (B)	62	99.6	160–162 (A)[c]	C,H,N
13	$C_{31}H_{25}ClN_4O_4 \cdot 0.3H_2O$	I	30	99.1	220–222 (A)[c]	C,H,N
14	$C_{24}H_{19}ClN_4O_4 \cdot 0.25H_2O$	I (B)	58	95.0	178–180 ($CHCl_3$)	C,H,N
15	$C_{25}H_{22}N_4O_4$	I (B)	81	95	207–210 ($CHCl_3$)	C,H,N
16	$C_{25}H_{23}N_3O_4 \cdot 0.05CH_2Cl_2$	I (B)	48	98.6	202–204 (CH_2Cl_2)	C,H,N
17	$C_{24}H_{19}ClN_6O_2 \cdot 0.75H_2O \cdot 2.25HOAc$	III	70	97.7	190 dec (A)[c]	C,H,N
18	$C_{26}H_{24}ClN_5O_3$	II (C)	43	98.2	293 dec (MeOH)	C,H,N
19	$C_{31}H_{26}ClN_5O_3$	II (C)	59	99.4	260–262 (MeOH)	C,H,N
20	$C_{28}H_{28}ClN_5O_3$	II (C)	40	99.9	284–285 (MeOH)	C,H,N
21	$C_{29}H_{30}ClN_5O_3$	II (C)	31	98.4	280–282 (Et_2O)	C,H,N
22	$C_{28}H_{28}ClN_5O_3 \cdot 0.25H_2O$	II (C)	40	98.5	173–175 (MeOH)	C,H,N
23	$C_{29}H_{31}N_5O_4 \cdot 0.25H_2O$	II (C)	73	99.5	222–224 (MeOH)	C,H,N
24	$C_{29}H_{29}N_5O_4$	II (C)	71	99.9	193–194 (MeOH)	C,H,N
25	$C_{28}H_{26}ClN_5O_3$	II (C)	20	99.9	264–266 (MeOH)	C,H,N
26	$C_{28}H_{26}ClN_5O_3 \cdot 0.1CHCl_3$	IV	84	96.3	192 (EtOAc–petroleum ether)	C,H,N
27	$C_{28}H_{26}ClN_5O_3 \cdot 0.7H_2O \cdot 0.05EtOAc$	IV	70	95.1	258 (EtOAc–MeOH)	C,H,N
28	$C_{29}H_{29}ClN_6O_3$	II (C)	48	99.9	278–280 (Et_2O)	C,H,N
29	$C_{30}H_{32}N_6O_4 \cdot 0.5H_2O$	II (C)	30	99.0	255–257 (MeOH)	C,H,N
30	$C_{30}H_{32}N_6O_3 \cdot HCl \cdot H_2O$	II (C)	20	97.6	226 dec (MeOH–Et_2O)	C,H,N
31	$C_{31}H_{35}IN_6O_3 \cdot 0.75H_2O$	II[d]	85	98.1	289 dec (Et_2O)	C,H,N
32	$C_{30}H_{26}N_6O_3 \cdot H_2O$	II (C)	40	99.5	222 dec (MeOH–H_2O)	C,H,N
33	$C_{30}H_{26}N_6O_3 \cdot 0.25H_2O$	II (C)	30	99.4	242 dec (MeOH–H_2O)	C,H,N
34	$C_{31}H_{31}N_5O_6$	II (C)	26	96.0	150–152 (A)[c]	C,H,N[e]
35	$C_{30}H_{29}N_5O_5 \cdot 0.5H_2O$	II[f]	29	98.4	192 dec (Et_2O–petroleum ether)	C,H,N[g]
36	$C_{25}H_{24}N_4O_3 \cdot 0.4H_2O \cdot 0.07Et_2O$	III	25	99.7	138–154[h] (Et_2O)	C,H,N
37	$C_{27}H_{29}N_5O_2 \cdot 0.75H_2O$	III	85	99.0	201–203 (EtOAc)	C,H,N
38	$C_{27}H_{29}N_5O_3$	III	68	99.3	213–215 (Et_2O)	C,H,N
39	$C_{28}H_{32}IN_5O_3$	III	67	99.8	258–260 (acetone)	C,H,N
40	$C_{25}H_{23}ClN_4O_4 \cdot 0.05CHCl_3$	III	65	99.9	232–234 (A)[c]	C,H,N
41	$C_{25}H_{22}Cl_2N_4O_3 \cdot 0.15CHCl_3 \cdot 0.15MeOH$	III	28	93.0	225 dec (MeOH)	C,H,N
42	$C_{27}H_{28}ClN_5O_3 \cdot 0.15CHCl_3$	III	56	96.5	219–221 (A)[c]	C,H,N
43	$C_{29}H_{30}ClN_5O_3$	III	22	99.8	206 dec (MeOH–Et_2O)	C,H,N
44	$C_{27}H_{24}N_6O_2 \cdot 0.35CHCl_3 \cdot 0.95H_2O$	III	41	97.6	240 dec (A)[c]	C,H,N[i]
45	$C_{27}H_{24}N_6O_2 \cdot 0.15CHCl_3 \cdot 1.15H_2O$	III	26	95.8	160 dec (A)[c]	C,H,N
46	$C_{27}H_{25}N_7O_2 \cdot 0.3CHCl_3 \cdot 0.85MeOH$	III	23	95.0	172 dec (A)[c]	C,H,N
47	$C_{31}H_{35}N_5O_4$	III	50	92.8[j]	97–104 (Et_2O)	C,H,N
48	$C_{29}H_{28}N_4O_6$	III	63	99.8	162–165 (CH_2Cl_2)	C,H,N
49	$C_{17}H_{15}FN_4O_2$	V (D)	95	99.3	205–207 (EtOAc)	C,H,N
50	$C_{21}H_{24}N_4O_2$	V (A)	45	100	281–282 (THF)	C,H,N
51	$C_{23}N_{26}N_4O_2$	V (A)	57	98.4	287–288 (THF)	C,H,N
52	$C_{23}N_{20}N_4O_2$	V (A)	60	99.4	260–261 (THF)	C,H,N
53	$C_{24}N_{22}N_4O_2$	V (A)	52	99.6	240–242 (THF)	C,H,N
54	$C_{25}H_{24}N_4O_2 \cdot 0.2THF$	V (A)	36	99.6	146–150 (Et_2O)	C,H,N
55	$C_{23}H_{19}ClN_4O_2$	V (A)	86	100	268–269 (MeOH)	C,H,N
56	$C_{23}H_{19}ClN_4O_2$	V (A)	94	97.3	206–208 (MeOH)	C,H,N
57	$C_{23}H_{19}ClN_4O_2$	V (A)	85	100	206–208 (MeOH)	C,H,N
58	$C_{23}H_{19}ClN_4O_2$	V (A)	75	99.2	233–234 (THF)	C,H,N
59	$C_{23}H_{19}ClN_4O_2 \cdot 0.2H_2O$	V (A)	55	94	178–180 (Et_2O–petroleum ether)	C,H,N
60	$C_{23}H_{19}ClN_4O_2$	V (A)	73	99.8	222 (MeOH)	C,H,N
61	$C_{23}H_{19}ClN_4O_2$	V (A)	85	99.8	223 (Et_2O–petroleum ether)	C,H,N
62	$C_{23}H_{18}Cl_2N_4O_2$	V (A)	51	98.9	285–287 (THF)	C,H,N
63	$C_{23}H_{18}Cl_2N_4O_2$	V (A)	66	99.8	274–276 (THF)	C,H,N
64	$C_{23}H_{19}FN_4O_2$	V (A)	25	100	269–270 (THF)	C,H,N
65	$C_{23}H_{19}FN_4O_2$	V (A)	93	99.6	252–254 (THF)	C,H,N
66	$C_{23}H_{19}BrN_4O_2$	V (A)	75	98.9	219–221 (MeOH)	C,H,N
67	$C_{23}H_{19}BrN_4O_2$	V (A)	43	93	286–287 (THF)	C,H,N
68	$C_{23}H_{19}BrN_4O_2$	V (A)	34	99.6	194–196 (Et_2O–petroleum ether)	C,H,N
69	$C_{23}H_{19}IN_4O_2$	V (A)	98	98	173–175 (Et_2O)	C,H,N
70	$C_{23}H_{19}N_5O_4$	V (A)	83	100	292–293 (THF)	C,H,N
71	$C_{23}H_{19}N_5O_4$	V (A)	68	99.8	288–289 (THF)	C,H,N
72	$C_{23}H_{19}N_5O_4$	V (A)	31	99.6	260–261 (THF)	C,H,N
73	$C_{24}H_{22}N_4O_3$	V (A)	88	98.9	261–263 (THF)	C,H,N
74	$C_{24}H_{22}N_4O_3$	V (A)	63	99.8	245–246 (THF)	C,H,N
75	$C_{25}H_{24}N_4O_4$	V (D)	17	97.9	267–269 (MeOH)	C,H,N
76	$C_{24}H_{22}N_4O_3$	V (A)	90	98.7	216–219 (Et_2O)	C,H,N
77	$C_{24}H_{22}N_4O_3$	V (A)	95	99.2	216–219 (Et_2O)	C,H,N
78	$C_{24}H_{22}N_4O_3 \cdot 0.5H_2O$	V (D)	44	99.7	258–260 (Et_2O)	C,H,N
79	$C_{24}H_{22}N_4O_2$	V (A)	89	99.7	274–277 (THF)	C,H,N
80	$C_{24}H_{22}N_4O_2$	V (A)	33	98.1	233–235 (Et_2O–petroleum ether)	C,H,N
81	$C_{24}H_{22}N_4O_2$	V (A)	85	98.5	158–160 (Et_2O–petroleum ether)	C,H,N
82	$C_{23}H_{20}N_4O_2 \cdot 0.5H_2O$	V (A)	78	100	165–180 (Et_2O)	C,H,N

Table VI. (Continued)

no.	formula	Scheme (method)	yield, %[a]	% purity HPLC	mp, °C (solvent[b])	analysis
83	$C_{25}H_{24}N_4O_2$	V (D)	92	100	165–167 (MeOH)	C,H,N
84	$C_{25}H_{24}N_4O_2$	V (D)	88	100	195–198[k] (MeOH)	C,H,N
85	$C_{24}H_{19}F_3N_4O_2 \cdot 0.5H_2O$	V (A)	35	99.2	174–176 (Et_2O)	C,H,N
86	$C_{24}H_{19}F_3N_4O_2$	V (A)	26	99.0	149 (Et_2O–petroleum ether)	C,H,N
87	$C_{26}H_{24}N_4O_2$	V (D)	34	98.4	156–158 (Et_2O)	C,H,N
88	$C_{25}H_{22}N_4O_2 \cdot 0.3H_2O \cdot 0.05EtOAc$	V (E)	82	100	212–214 (Et_2O)	C,H,N
89	$C_{25}H_{20}N_4O_2 \cdot 0.4EtOAc$	V (E)	78	97.6	164–165 (EtOAc–hexane)	C,H,N
90	$C_{29}H_{24}N_4O_2 \cdot 0.2H_2O$	V (D)	44	97.5	255–256 (EtOAc)	C,H,N
91	$C_{24}H_{22}N_4O_3 \cdot 0.6H_2O$	V (D)	50	96.4	166–168 (A)[c]	C,H,N
92	$C_{26}H_{26}N_4O_3 \cdot 0.3H_2O \cdot 0.45EtOAc$	V[l]	15	98.1	145 (EtOAc)	C,H,N
93	$C_{25}H_{22}N_4O_3 \cdot 0.35H_2O$	V (A)	89	100	225–226 ($CHCl_3$)	C,H,N
94	$C_{23}H_{20}N_4O_3 \cdot 0.55EtOAc$	V	78	100	208–210 (A)[c]	C,H,N
95	$C_{25}H_{22}N_4O_4$	V (D)	77	96.4	148 (Et_2O)	C,H,N
96	$C_{23}H_{21}N_5O_2 \cdot 0.65H_2O$	V (D)	40	99.6	174–175 (EtOAc–MeOH)	C,H,N
97	$C_{29}H_{31}N_5O_4 \cdot 0.3H_2O$	V (D)	55	99.4	173–175 (EtOAc–hexane)	C,H,N
98	$C_{29}H_{25}N_5O_2$	V (D)	71	99.2	172–175 (EtOAc–Et_2O)	C,H,N
99	$C_{24}H_{23}N_5O_2 \cdot 2HCl \cdot 0.3H_2O \cdot 0.25EtOAc$	V	95	96.9	226 (EtOAc–MeOH)	C,H,N
100	$C_{24}H_{19}N_5O_2 \cdot 0.25H_2O$	V (A)	86	98.7	249–250 (EtOAc–MeOH)	C,H,N
101	$C_{24}H_{20}N_4O_4$	V (D)	51	98.6	210 (EtOAc–MeOH)	C,H,N
102	$C_{24}H_{20}N_4O_4 \cdot 1.15H_2O$	V (D)	52	98.3	175–180 (MeOH)	C,H,N
103	$C_{25}H_{22}N_4O_4$	V (D)	44	98.3	210 (MeOH)	C,H,N
104	$C_{26}H_{24}N_4O_4$	V (D)	93	98.8	151–153 (EtOAc)	C,H,N
105	$C_{25}H_{22}N_4O_4$	V	90	97.2	167–170 (EtOAc)	C,H,N
106	$C_{27}H_{22}N_4O_2$	V (A)	66	98.4	234–235 (THF)	C,H,N
107	$C_{24}H_{20}N_4O_4 \cdot 0.6H_2O \cdot 0.2EtOAc$	V (E)	25	98.6	155 (A)[c]	C,H,N
108	$C_{23}H_{21}N_5O_2 \cdot 0.15H_2O$	VI (A)	77	99.9	248–251 (MeOH)	C,H,N
109	$C_{23}H_{21}N_5O_2 \cdot 0.4H_2O$	VI (A)	76	95.9	252–254 (THF)	C,H,N
110	$C_{23}H_{21}N_5O_2 \cdot 0.65H_2O$	VI (A)	72	99.0	162–165 (A)[c]	C,H,N
111	$C_{23}H_{21}N_5O_2 \cdot H_2O \cdot 0.4Et_2O$	VI (A)	31	95.3	201–209 (Et_2O)	C,H,N
112	$C_{23}H_{21}N_5O_2 \cdot 0.95H_2O$	VI (A)	28	99.6	251–253 ($CHCl_3$–MeOH)	C,H,N
113	$C_{23}H_{21}N_5O_2 \cdot 0.38MeOH$	VI (A)	10	99.3	225–236 (CH_2Cl_2–MeOH)	C,H,N[m]
114	$C_{28}H_{30}N_6O_3 \cdot 0.15Et_2O \cdot 0.5EtOAc$	VI (A)	74	98.9	201–207 (Et_2O)	C,H,N
115	$C_{22}H_{19}N_5O_2$	V (D)	40	99.3	232–233 (Et_2O)	C,H,N
116	$C_{22}H_{19}N_5O_2 \cdot 0.07THF$	V (D)	52	97.7	274–275 (THF)	C,H,N
117	$C_{22}H_{19}N_5O_2$	V (D)	57	95.7	162–173[n] (CH_2Cl_2–Et_2O)	C,H,N
118	$C_{22}H_{20}N_6O_2 \cdot H_2O$	V (D)	20	97.8	176–184 (CH_2Cl_2–MeOH)	C,H,N
119	$C_{23}H_{21}N_5O_3 \cdot 0.35H_2O \cdot 0.25THF$	V (A)	89	98.2	168–170 (EtOAc)	C,H,N
120	$C_{22}H_{18}ClN_5O_2 \cdot 0.35H_2O \cdot 0.15THF$	V (E)	70	99.0	130(d) (EtOAc–hexane)	C,H,N
121	$C_{26}H_{21}N_5O_2 \cdot 0.05Et_2O$	V (D)	32	99.9	250–251 (Et_2O)	C,H,N
122	$C_{26}H_{21}N_5O_2 \cdot 0.5H_2O$	V (D)	11	99.5	249–254 (MeOH)	C,H,N

[a] Yield refers to the last synthetic step, is unoptimized, and represents analytically pure material. [b] Recrystallization or trituration solvent. [c] Amorphous material obtained directly via chromatography. [d] Heat **30** with iodomethane in acetone, 1 h. [e] Calcd: N, 12.30. Found: N, 11.23. [f] From **34**, 1 N NaOH, THF, 23 °C. [g] Calcd: N, 12.76. Found: N, 11.85. [h] Gas evolution. [i] Calcd: N, 16.06. Found: N, 15.06. [j] Contains 5.5% **36**. [k] Sinter at 175 °C. [l] **93** and MeMgBr, THF, 0 °C. [m] Calcd: N, 17.02. Found: N, 15.91. [n] Foam.

elemental analysis; the occurrence of solvation was confirmed independently by ^1H NMR spectroscopy.

Flash chromatography was performed on silica gel (E. Merck 40–63 mm) as described by Still.[37] Thin-layer chromatography (TLC) and preparative thick-layer chromatography (PLC) were carried out on E. Merck 60F-254 precoated silica gel plates (0.25, 0.5, and 2-mm thickness) using UV_{254} light, iodine vapors, or 5% phosphomolybdic acid reagent in 95% ethanol to visualize the developed plates. All reactions, except those performed in aqueous solvents, were carried out with use of standard techniques for the exclusion of moisture. Commercial chemicals were used as obtained without purification, except for solvents, which were purified and dried, where appropriate, before use by standard methods.

(*R,S*)-*N*-(5-(2-Fluorophenyl)-2,3-dihydro-2-oxo-2*H*-1,4-benzodiazepin-3-yl)-*N'*-(4-chlorophenyl)urea (7). Method A. Equimolar amounts of 3(*R,S*)-amino-1,3-dihydro-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one (85 mg) and *p*-chlorophenyl isocyanate (40 μL) were combined in 8 mL of dry THF at room temperature. The reaction mixture was allowed to stand undisturbed overnight, and the resulting solid was collected. Trituration with methanol afforded 115 mg (86%) of the analytical sample: mp 278 °C; ^1H NMR (DMSO-d_6) δ 4.04 (br s, 1H), 5.18 (d, 1H, C*H*NH), 7.22 (m, 3H), 7.3 (m, 4H), 7.42 (t, 1H), 7.43 (d, 1H, CHN*H*CO), 7.56 (m, 4H), 9.20 (s, 1H); MS *m/e* 422 (M^+), 295, 269 (100), 153. Anal. ($C_{22}H_{16}ClFN_4O_2$) C, H, N.

Ethyl 3-[(Benzyloxycarbonyl)amino]-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetate (IIIa). To an ice-cold suspension of sodium hydride (432 mg, 9 mmol, 50% oil dispersion) in 50 mL of dry DMF was added **Ia** (3 g, 7.8 mmole) in one portion, under nitrogen. After 2 h, ethyl bromoacetate (993 μL, 9 mmol) was added dropwise to the homogeneous reaction mixture. The reaction mixture was warmed to room temperature over 1 h. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (hexane/ethyl acetate, 3:2, v/v) afforded 3.22 g (87%) of the analytical material: mp 65–66 °C; R_f = 0.5 (hexane–ethyl acetate, 1:1); ^1H NMR ($CDCl_3$) δ 1.17 (t, 3H), 4.15 (q, 2H), 4.60 (AB q, 2H, CH_2CO_2Et), 5.15 (AB q, 2H, OCH_2Ph), 5.45 (d, 1H, C*H*NH), 6.67 (d, 1H, CHN*H*CO), 7.27 (m, 2H), 7.31–7.43 (m, 6H), 7.47 (m, 2H), 7.58 (m, 2H), 7.64 (m, 2H); FAB MS 472 (M^+ + H). Anal. ($C_{27}H_{25}N_3O_5$) C, H, N.

Ethyl 3(*R,S*)-{[((4-Chlorophenyl)amino)carbonyl]amino}-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetate (9). Method B. The Cbz-benzodiazepine **IIIa** (1.47 g, 3.1 mmol) was dissolved in 60 mL of methanol containing 90% formic acid (4.5% by volume). This solution was added to a suspension of 740 mg of palladium/carbon (10%) catalyst in the above solvent system under nitrogen. The resulting reaction mixture was stirred 1.5 h and then carefully filtered through Celite. The recovered catalyst was washed with methanol, and the combined filtrate and washings were concentrated in vacuo to afford ethyl 3(*R,S*)-amino-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetate formate salt in quantitative yield (R_f = 0.11, $CHCl_3/CH_3OH$/concentrated NH_4OH, 95:5:0.5, v/v). This material (510 mg, 1.33 mmol) was taken without further purification, dissolved in 40 mL of THF containing 256 μL (1.84 mmole) of triethylamine, and converted to **9** in 1 h with *p*-chlorophenyl isocyanate according to method A (76% yield): mp 228–229 °C; R_f = 0.45 ($CHCl_3$/

CH_3OH/concentrated NH_4OH, 95:5:0.5); ^1H NMR ($CDCl_3$) δ 1.16 (t, 3H), 4.13 (m, 2H, $CO_2CH_2CH_3$), 4.62 (AB q, 2H, CH_2CO_2Et), 5.66 (d, 1H, CHNH), 6.89 (d, 1H, CHNHCO), 6.97 (br s, 1H, CONHAr), 7.18 (m, 2H), 7.26 (m, 3H), 7.38 (m, 4H), 7.46 (ddd, 1H), 7.59 (ddd, 1H), 7.65 (m, 2H); FAB MS 491 ($M^+ + H$). Anal. ($C_{26}H_{23}ClN_4O_4$) C, H, N.

3(*R,S*)-{[((4-Chlorophenyl)amino)carbonyl]amino}-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetic Acid (14). The ester **9** (550 mg, 1.12 mmol) was added to a mixture of 10 mL of THF and 1 N sodium hydroxide solution (4 mL) at 23 °C. The resulting solution was stirred for 3 h, acidified with 6 N HCl, and concentrated to a 10-mL volume. The reaction mixture was extracted with ethyl acetate, and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The analytical sample was obtained in 58% yield after flash chromatography ($CHCl_3/CH_3OH$/HOAc, 90:10:1)and crystallization from $CHCl_3$: mp 178–180 °C; R_f = 0.26 ($CHCl_3/CH_3OH$/HOAc, 90:10:1); ^1H NMR (DMSO-d_6) δ 4.69 (AB q, 2H), 5.32 (d, 1H, CHNH), 7.25–7.6 (m, 12H), 7.63 (d, 1H), 7.71 (t, 1H), 9.21 (br s, 1H); FAB MS 463 ($M^+ + H$). Anal. ($C_{24}H_{19}ClN_4O_4 \cdot 0.25H_2O$) C, H, N.

Benzyl 3(*R,S*)-{[((4-Chlorophenyl)amino)carbonyl]amino}-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetate (13). The acid **14** (100 mg, 0.22 mmol) and benzyl alcohol (25 μL, 0.24 mmol) were combined in 2 mL of methylene chloride with dicyclohexylcarbodiimide (50 mg, 0.24 mmol) at room temperature. After 2 h, the reaction mixture was filtered; the filtrate was concentrated to half its volume and applied directly to two precoated SiO_2 PLC plates. Methylene chloride–acetone elution (95:5) afforded the analytical sample: mp 220–222 °C; R_f = 0.36 (CH_2Cl_2/acetone, 95:5); ^1H NMR (DMSO-d_6) δ 4.70 (AB q, 2H), 5.1 (s, 2H), 5.7 (d, 1H, CHNH), 7.05 (d, 1H), 7.1–7.5 (m, 17H), 7.60 (d, 1H), 7.65 (t, 1H); FAB MS 553 ($M^+ + H$). Anal. ($C_{31}H_{25}ClN_4O_4 \cdot 0.3H_2O$) C, H, N.

***N,N*-Diethyl-3(*R,S*)-[(benzyloxycarbonyl)amino]-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetamide (IV). Method C.** The ester **IIIa** (3.1 g, 6.6 mmol) was saponified according to the procedure for the preparation of **14**. Trituration of the crude reaction product with ethyl ether containing methanol (10:1, v/v) gave the corresponding acid in 93% yield (R_f = 0.3, $CHCl_3/CH_3OH$/HOAc, 90:10:1). A portion of this material (900 mg, 2.0 mmol) was suspended in 20 mL of toluene and treated with 2 mL of thionyl chloride. The resulting mixture was heated to 90 °C for 1 h, cooled, and concentrated under reduced pressure. The residue was redissolved in toluene and concentrated; this cycle was repeated twice more to afford the acid chloride (900 mg, 96%) in sufficient purity to be carried on directly to the next step. The acid chloride (265 mg, 0.57 mmol) in 5 mL of dry THF was then treated with 124 μL (1.2 mmol) of diethylamine at 23 °C. After 1 h, the reaction mixture was rotoevaporated to dryness, the residue was dissolved in ethyl acetate, and this solution was washed with water. The organic phase was dried and concentrated to yield 250 mg (88%) of **IV**: mp 153–154 °C; R_f = 0.14 (CH_2Cl_2/acetone, 95:5); ^1H NMR ($CDCl_3$) δ 1.14 (t, 3H), 1.25 (t, 3H), 3.34 (m, 2H), 3.44 (m, 2H), 4.37 (d, 1H, CH_2CONEt_2, J = 17 Hz), 4.85 (d, 1H, CH_2CONEt_2, J = 17 Hz), 5.15 (AB q, 2H), 5.45 (d, 1H, CHNH), 6.75 (d, 1H, CHNHCO), 7.25 (t, 1H), 7.3–7.42 (m, 7H), 7.46 (m, 3H), 7.55 (t, 1H), 7.63 (m, 2H); FAB MS 499 (M + + H). Anal. ($C_{29}H_{30}N_4O_4 \cdot 0.5H_2O$) C, H, N.

***N,N*-Diethyl-3(*R,S*)-{[((3-methoxyphenyl)amino)carbonyl]amino}-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetamide (23).** The Cbz protecting group in **IV** was removed using reaction conditions identical to those described for the synthesis of **9**. In this way, 600 mg (1.2 mmol) of **IV** was converted to 480 mg (97%) of the corresponding amine formate salt. A portion of the amine salt (100 mg, 0.24 mmol) was then reacted with *m*-methoxyphenyl isocyanate (32 μL, 0.24 mmol) according to method A, yielding **23** as a white solid (90 mg, 73%) after PLC chromatography ($CHCl_3/CH_3OH$/concentrated NH_4OH, 97:3:0.3) and trituration with methanol: mp 222–224 °C; R_f = 0.27 ($CHCl_3/CH_3OH$/concentrated NH_4OH, 95:5:0.5); ^1H NMR ($CDCl_3$) δ 1.0 (t, 3H), 1.12 (t, 3H), 3.25 (m, 2H), 3.44 (m, 2H), 3.69 (s, 3H), 4.79 (AB q, 2H), 5.32 (d, 1H, CHNH), 6.51 (dd, 1H), 6.83 (m, 1H), 7.15 (m, 2H), 7.30 (dd, 1H), 7.35 (t, 1H), 7.45–7.55 (m, 7H), 7.69 (dd, 1H), 9.05 (s, 1H); FAB MS 514 ($M^+ + H$). Anal. ($C_{29}H_{31}N_5O_4 \cdot 0.25H_2O$) C, H, N.

(*R,S*)-*N*-(2,3-Dihydro-1-(2-tetrazolylmethyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(4-chlorophenyl)urea (17). The benzodiazepine **Ia** (500 mg, 1.3 mmol) was metalated with sodium hydride (1.56 mmol) in 8 mL of DMF at 0 °C and alkylated with chloroacetonitrile (95 μL, 1.56 mmol) in the usual manner. Flash chromatography (hexane–ethyl acetate, 2:1) of the crude reaction product gave 360 mg of the corresponding 1-cyanomethyl adduct; R_f = 0.48 (hexane–ethyl acetate, 2:1). This material (150 mg, 0.38 mmol) was mixed with sodium azide (124 mg, 1.90 mmol) and ammonium chloride (102 mg, 1.90 mmol) in 3 mL of dry DMF and heated at 110 °C for 4 h. The reaction mixture was concentrated, and the residue was suspended in water and acidified with 1 N HCl. Extractive workup with ethyl acetate and PLC chromatography ($CHCl_3$/MeOH/HOAc, 90:10:1) gave 99 mg (57%) of the tetrazole which was immediately deprotected with HBr gas in methylene chloride at 0 °C for 1 h. The resulting hydrobromide salt was azeotropically dried with toluene to yield 110 mg of crude product. Without further purification, 55 mg (0.105 mmol) of the amine hydrobromide salt was dissolved in 2 mL of THF containing 36.5 μL (0.262 mmol) of triethylamine. To this solution was added 16.1 mg (0.105 mmol) of *p*-chlorophenyl isocyanate at room temperature. The reaction was filtered after 1 h, and the solids were purified via PLC chromatography ($CHCl_3$/MeOH/HOAc, 90:10:1) to afford 35 mg (70%) of **17**: mp >190 °C dec; R_f = 0.15 ($CHCl_3$/MeOH/HOAc, 90:10:1); ^1H NMR (DMSO-d_6) δ 5.41 (d, 1H), 5.42 (d, 1H, CHNH), 5.47 (d, 1H), 7.25–7.55 (m, 13H), 7.59 (t, 1H), 7.80 (d, 1H), 9.2 (br s, 1H); FAB MS 487 ($M^+ + H$). Anal. ($C_{24}H_{19}ClN_8O_2 \cdot 2.25HOAc \cdot 0.75H_2O$) C, H, N.

(*R,S*)-*N*-(2,3-Dihydro-1-(2-hydroxyethyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3-methylphenyl)urea (36). The benzodiazepine **Ia** (1.4 g, 3.63 mmol) in 20 mL of DMF was added to a suspension of sodium hydride (183 mg, 3.81 mmol, 50% oil dispersion) in 5 mL of DMF at 0 °C. After 0.5 h, 1.6 mL of a DMF solution containing oxirane (100 mg/mL) was added in one portion, and the reaction mixture was warmed on a steam bath for 0.5 h. Thereafter, 3.2 mL of the same DMF/oxirane solution was added at 0.5-h intervals three more times. After the last addition, the reaction mixture was warmed for 1 h and then all volatiles were removed *in vacuo*. The residue was treated with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and flash chromatographed (35% EtOAc/CH_2Cl_2). The chromatographed product was crystallized from ether to give 720 mg of analytically pure material: mp 150–152 °C; R_f = 0.38 (40% EtOAc/CH_2Cl_2). This material (600 mg, 1.40 mmol) was deprotected with HBr gas in the usual manner and after alkaline workup gave 366 mg of 1,3-dihydro-1-(2-hydroxyethyl)-3-(*R,S*)-amino-5-phenyl-1*H*-1,4-benzodiazepin-2-one. The latter compound (300 mg, 1.02 mmol) was combined with 250 μL of *m*-tolyl isocyanate in 10 mL of THF at ambient temperature. The pH of the reaction mixture was adjusted to 9.5 with the addition of triethylamine. After 1 h the reaction mixture was filtered, the filtrate was flash chromatographed (20% acetone/CH_2Cl_2), and the resultant product was crystallized from ethyl ether to yield 77 mg (25%) of **36**: mp 138–154 °C (slow decomposition); R_f = 0.24 (CH_2Cl_2/MeOH/H_2O/HOAc, 90:4:0.4:0.4); ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.30 (t, 1H, OH), 3.78 (m, 2H), 3.94 (ddd, 1H), 4.22 (ddd, 1H), 5.57 (d, 1H, CHNH), 6.8–6.9 (m, 3H), 7.1–7.4 (m, 8H), 7.45 (t, 1H), 7.58 (m, 4H); FAB MS 429 ($M^+ + H$). Anal. ($C_{25}H_{24}N_4O_3 \cdot 0.07Et_2O \cdot 0.4H_2O$) C, H, N.

(*R,S*)-*N,N*-Diethyl-2-(2,3-dihydro-3-{[((3-methylphenyl)amino)carbonyl]amino})-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-1-yl)glycine Ethyl Ester (47). A solution of *N,N*-diethylglycine hydrochloride (215 mg, 2.56 mmol) in 20 mL of DMF was treated sequentially with 1-hydroxybenzotriazole hydrate (HBT) (173 mg, 2.56 mmol), 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC) (245 mg, 2.56 mmol), and triethylamine (178 μL, 2.56 mmol). After 30 min at room temperature, approximately half of this stock solution was then added to a solution of DMF (20 mL) containing 55 mg (0.128 mmol) of **36**. The reaction mixture was stirred 4 h at ambient temperature, and more of the stock solution (ca. 25%) was added to drive the reaction to completion (overnight stirring; pH of the reaction mixture = 9). The solvent was rotoevaporated, and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The combined organic extracts

were washed with brine, dried (Na_2SO_4), concentrated, and flash chromatographed (CH_2Cl_2/MeOH/H_2O/HOAc, 90:5:0.5:0.5) to yield 41 mg of semipure product. Rechromatography (PLC, 10% hexane–ethyl acetate) of this material afforded a semisolid which was triturated with Et_2O to give **47** in 50% yield: mp 97–104 °C (slow decomposition); R_f = 0.32 (CH_2Cl_2/MeOH/H_2O/HOAc, 90:10:1:1); ^1H NMR ($CDCl_3$) δ 1.18 (t, 6H), 2.30 (s, 3H), 2.95 (br s, 4H), 3.46 (AB q, 2H), 3.89 (ddd, 1H), 4.20 (m, 2H), 4.76 (m, 1H), 5.56 (d, 1H, C*H*NH), 6.85 (d, 1H), 6.70 (d, 1H, CHN*H*), 7.15 (t, 1H), 7.2–7.5 (m , 8H), 7.6 (m, 4H); FAB MS 542 (M^+ + H). Anal. ($C_{31}H_{35}N_5O_4$) C, H, N.

(*R,S*)-2-(2,3-Dihydro-3-{[((3-methylphenyl)amino)carbonyl]amino}-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-1-yl)ethyl Butanedioic Acid Monoester (48). A solution of **36** (40 mg, 0.093 mmol) in 3 mL of methylene chloride was treated with 11 mg, 0.11 mmol) of succinic anhydride and 13.4 mg (0.11 mmol) of 4-(dimethylamino)pyridine (DMAP) at room temperature. After 4 h, more succinic anhydride (4.1 mg) and DMAP (5.0 mg) were added, and the reaction mixture was stirred overnight. The reaction mixture was diluted with methylene chloride, washed with 1 N HCl solution, water, and brine, and then concentrated to yield a foam. Chromatography (4% MeOH/CH_2Cl_2) of this material gave a foam which was crystallized from methylene chloride to afford 31 mg (63%) of **48**: mp 162–165 °C; R_f = 0.47 (10% MeOH/CH_2Cl_2); ^1H NMR (DMSO-d_6) δ 1.88 (m, 1H), 2.06 (m, 1H), 2.33 (m, 2H), 2.24 (s, 3H), 4.02 (m, 3H), 4.56 (m, 1H), 5.26 (d, 1H, C*H*NH), 6.74 (d, 1H), 7.12 (t, 1H), 7.15 (d, 1H), 7.22 (br s, 1H), 7.36 (t, 1H), 7.4–7.55 (m, 8H), 7.75 (m, 2H), 9.0 (s, 1H); MS *m/e* 529 (M^+), 422, 396, 379 (100), 351. Anal. ($C_{29}H_{28}N_4O_6$) C, H, N.

(*R,S*)-2,3-Dihydro-3-{[((3-methoxyphenyl)aminocarbonyl]amino)}-*N,N*-dimethyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-ethanamine (38). 2-(Dimethylamino)ethyl chloride was prepared by vacuum distillation (23–25 °C (24 Torr)), of an intimate mixture of 2-(dimethylamino)ethyl chloride hydrochloride and crushed sodium hydroxide pellets. The distillate was stored over potassium hydroxide pellets, decanted, and dried with calcium hydride. A freshly prepared sample of 2-(dimethylamino)ethyl chloride (59.2 mg, 0.55 mmol) was then added neat to 210 mg (0.545 mmol) of the sodium enolate of **Ia** in 4 mL of DMF at 0 °C. The reaction mixture was warmed to room temperature and stirred for 48 h. The solvent was rotoevaporated, and the residue was flash chromatographed (CH_2Cl_2/MeOH/H_2O/HOAc, 90:10:1:1). The pooled product-containing fractions were concentrated, and the product was partitioned between ethyl acetate and 10% sodium carbonate solution. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to give 120 mg of the N^1-adduct. This material was then elaborated to **38** by removal of the Cbz group according to method B and final urea formation with *m*-methoxyphenyl isocyanate following the procedure of method A: mp 213–215 °C; R_f = 0.41 (CH_2Cl_2/MeOH/concentrated NH_4OH, 80:10:1); ^1H NMR (DMSO-d_6) δ 1.90 (br s, 6H), 2.28 (br t, 2H, CH_2NMe$_2$), 3.69 (s, 3H, OCH_3), 3.86 (ddd, 1H), 4.37 (ddd, 1H), 5.24 (d, 1H, C*H*NH), 6.51 (dd, 1H), 6.85 (dd, 1H), 7. 14 (t, 1H), 7.15 (d, 1H), 7.30 (d, 1H), 7.36 (t, 1H), 7.45–7.55 (m, 6H), 7.70 (t, 1H), 7.78 (d, 1H), 9.05 (s, 1H); FAB MS 472 (M^+ + H). Anal. ($C_{27}H_{29}N_5O_3$) C, H, N.

(*R,S*)-2,3-Dihydro-3-{[((3-methoxyphenyl)aminocarbonyl]amino}-*N,N,N*-trimethyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-ethanaminium Iodide (39). The amine **38** (25 mg, 0.053 mmol) was dissolved in 10 mL of warm acetone and treated with 16.5 μL of iodomethane. The reaction mixture was refluxed for 1 h, treated with an additional 10 μL of iodomethane, and heated for 1 h more. The reaction mixture was allowed to stand at ambient temperature overnight whereupon the product precipitated from solution: mp 258–260 °C; ^1H NMR (DMSO-d_6) δ 3.38 (br s, 9H), 3.45 (m, 1H), 3.56 (m, 1H), 3.69 (s, 3H), 4.34 (m, 1H), 4.54 (m, 1H), 5.29 (d, 1H, C*H*NH), 6.56 (dd, 1H), 6.82 (dd, 1H), 7.14 (t, 1H), 7.15 (d, 1H), 7.37 (d, 1H), 7.45–7.6 (m, 7H), 7.80 (m, 2H), 9.05 (s, 1H); FAB MS 486 (M^+ + H), 236 (100). Anal. ($C_{28}H_{32}IN_5O_3$) C, H, N.

(*R,S*)-*N*-(2,3-Dihydro-1-(2-(*S*)-oxiranylmethyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(4-chlorophenyl)-urea (V). The benzodiazepine **Ia** (1.52 g, 3.94 mmol) was metalated with sodium hydride (190 mg, 4.73 mmol, 60% oil dispersion) in 10 mL of DMF at 0 °C for 1 h and alkylated with (2*S*)-(+)-glycidyl-3-nitrobenzenesulfonate (1.23 g, 4.74 mmol). Extractive workup with ethyl acetate and flash chromatography (ethyl acetate–hexane, 4:1) of the resultant crude product gave 1.7 g (98%) of the N^1-alkylated product as a mixture of diastereomers. Removal of the Cbz-protecting group according to method B and reaction of the resulting amine with *p*-chlorophenyl isocyanate following the procedure of method A gave **V** (mixture of diastereomers) in 72% yield after chromatography ($CHCl_3$/MeOH/concentrated NH_4OH, 90:10:1) and recrystallization (EtOAc): mp 228–230 °C dec; ^1H NMR (DMSO-d_6) all envelopes in the aliphatic region are doubled δ 2.40 (dd, 1H), 2.47 (dd, 1H), 2.66 (t, 1H), 2.67 (t, 1H), 2.96 (ddd, 1H), 3.16 (ddd, 1H), 3.8 (dd, 1H), 3.97 (dd, 1H), 4.32 (dd, 1H), 4.46 (dd, 1H), 5.25 (d, 1H, C*H*NH), 5.26 (d, 1H, C*H*NH), 7.26–7.8 (m, 28H, Ar & CHN*H*), 9.20 (br s, 2H); FAB MS 461 (M^+ + H). Anal. ($C_{25}H_{21}ClN_4O_3$) C, H, N.

(*R,S*)-*N*-(2,3-Dihydro-1-((2*S*)-1,2-dihydroxypropyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(4-chlorophenyl)-urea (40). Epoxide **V** (58 mg, 0.126 mmol) was dissolved in 1.5 mL of acetic acid containing 60 μL of water. The resulting solution was allowed to stand at room temperature for 18 h. All volatiles were removed under reduced pressure, and the residue was chromatographed (PLC, $CHCl_3$/MeOH, 88:12) to give 39 mg (65%) of **40** as a mixture of diastereomers: mp 232–234 °C; R_f = 0.18 ($CHCl_3$/MeOH/concentrated NH_4OH, 90:10:1); ^1H NMR (DMSO-d_6) shows all the expected resonances to be doubled; FAB MS 479 (M^+ + H). Anal. ($C_{25}H_{23}ClN_4O_4$·0.05$CHCl_3$) C, H, N.

(*R,S*)-*N*-(2,3-Dihydro-1-(1-hydroxy-2-chloropropyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(4-chlorophenyl)-urea (41). Epoxide **V** (135 mg, 0.293 mmol) was dissolved in 5 mL of pyridine, and this solution was treated with 60 mg (0.863 mmol) of hydroxylamine hydrochloride. The resulting mixture was stirred at room temperature for 60 h. The reaction mixture was filtered and concentrated in vacuo, and the residue was chromatographed (PLC, $CHCl_3$/MeOH/concentrated NH_4OH, 90:10:1) to yield 40 mg (29%) of **41** after crystallization from methanol: mp 225 °C dec; ^1H NMR (DMSO-d_6) shows all the expected resonances to be doubled; FAB MS 497 (M^+ + H). Anal. ($C_{25}H_{22}Cl_2N_4O_3$·0.15$CHCl_3$·0.15MeOH) C, H, N.

(*R,S*)-*N*-(2,3-Dihydro-1-(1-(dimethylamino)-2-hydroxypropyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(4-chlorophenyl)urea (42). A solution of the epoxide **V** (56 mg, 0.121 mmol) in 6 mL of THF was treated with a continuous stream of dimethylamine gas for 45 min at 0 °C. The reaction flask was capped, and the reaction mixture was allowed to warm to room temperature overnight (total reaction time = 60 h). All volatiles were removed in vacuo, and the residue was chromatographed (PLC, $CHCl_3$/MeOH/concentrated NH_4OH, 90:10:1) to yield 34 mg (56%) of **42**: mp 219–221 °C dec; R_f = 0.17 ($CHCl_3$/MeOH/concentrated NH_4OH, 90:10:1); ^1H NMR (DMSO-d_6) shows all the expected resonances to be doubled; FAB MS 506 (M^+ + H). Anal. ($C_{27}H_{28}ClN_5O_3$·0.15$CHCl_3$) C, H, N.

(*R,S*)-*N*-(2,3-Dihydro-1-(4-imidazolylmethyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3-methylphenyl)urea (44). The benzodiazepine **Ia** (186 mg, 0.483 mmol) was metalated with sodium hydride (0.531 mmol) in 4 mL of DMF at 0 °C for 1 h and alkylated with 1-(2,4-dinitrophenyl)-3-(chloromethyl)imidazole (150 mg, 0.531 mmol). After 1 h the reaction mixture was concentrated, and the residue was partitioned between ethyl acetate and 10% citric acid solution. The combined organic extracts were concentrated and flash chromatographed ($CHCl_3$–MeOH, 9:1) to give 200 mg of the N^1-alkylated product; R_f = 0.51 (ethyl acetate). Removal of the Cbz protecting group from the alkylation product (70 mg, 0.11 mmol) with HBr gas in methylene chloride at 0 °C for 0.5 h gave 70 mg of the hydrobromide salt after azeotropic drying with toluene. Without further purification, the urea was linkage was formed by combining 70 mg (0.105 mmol) of the amine hydrobromide salt with 15.9 μL (0.214 mmol) of *m*-tolyl isocyanate in 3 mL of THF containing 46.8 μL (0.336 mmol) of triethylamine. After 0.5 h the reaction mixture was filtered, and the filtrate was concentrated. The residual material was chromatographed (PLC, EtOAc) to yield 43 mg of the penultimate product. Final deprotection of the imidazole ring on 40 mg (0.063 mmol) of above-obtained material was effected with thiophenol (12 μL, 0.127 mmol) in 2 mL of DMF at 23 °C. The reaction mixture was filtered after 0.5 h,

concentrated, and purified via PLC chromatography ($CHCl_3$/MeOH, 95:5) to afford 12 mg (41%) of **44**: mp 240 °C dec; R_f = 0.44 ($CHCl_3$/MeOH, 9:1); ^1H NMR (DMSO-d_6) δ 2.21 (s, 3H), 4.92 (d, 1H), 5.12 (d, 1H, C*H*NH), 5.26 (d, 1H), 6.75 (d, 1H), 6.79 (br s, 1H), 7.11 (t, 1H), 7.13 (t, 1H), 7.2–7.5 (m, 10H), 7.68 (t, 1H), 8.0 (br s, 1H), 8.99 (s, 1H), 11.85 (br s, 1H); FAB MS 465 (M^+ + H). Anal. ($C_{27}H_{24}N_6O_2$·0.35$CHCl_3$·0.95H_2O) C, H, N.

(*R,S*)-*N*-(2,3-Dihydro-1-(2-imidazolylmethyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3-methylphenyl)urea (45). Prepared in identical fashion to **44**: mp 160 °C dec; R_f = 0.37 ($CHCl_3$/MeOH/concentrated NH_4OH, 90:10:1); ^1H NMR (DMSO-d_6) δ 2.25 (s, 3H), 5.11 (AB q, 2H), 5.31 (d, 1H, C*H*NH), 6.75 (d, 1H), 6.85 (br s, 1H), 7.11 (t, 1H), 7.15 (t, 1H), 7.2–7.55 (m, 10H), 7.68 (t, 1H), 7.90 (d, 1H), 8.99 (s, 1H); FAB MS 465 (M^+ + H). Anal. ($C_{27}H_{24}N_6O_2$·0.15$CHCl_3$·1.15H_2O) C, H, N.

(*R,S*)-*N*-(2,3-Dihydro-1-((2-methyl-1,3,4-triazol-5-yl)-methyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3-methylphenyl)urea (46). The benzodiazepine **Ia** (1.5 g, 3.89 mmol) was metalated with cesium carbonate (1.648 g, 5.06 mmol) in 15 mL of DMF at 0 °C for 0.25 h and treated with 2-chloroacetamide (573 mg, 6.12 mmol). The reaction mixture was stirred at room temperature for 2 h, filtered, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 10% citric acid solution. The combined organic extracts were dried and concentrated to yield 2.8 g of the N^1-acetamido adduct as an oil which crystallized on standing. Of this material, 138 mg (0.31 mmol) was heated at 100 °C with 2 mL of *N,N*-dimethylacetamide dimethyl acetal for 3 h. Extractive workup with ethyl acetate gave a semisolid which was combined with 27 μL of 95% hydrazine in 5 mL of glacial acetic acid at 90 °C. The reaction mixture was cooled, poured into water (50 mL), and extracted with ethyl acetate. The combined organic extracts were concentrated and purified via PLC chromatography ($CHCl_3$/MeOH, 94:6) to yield 113 mg of (*R,S*)-2,3-dihydro-1-((2-methyl-1,3,4-triazol-5-yl)methyl)-2-oxo-3-((benzyloxycarbonyl)amino)-5-phenyl-1*H*-1,4-benzodiazepin-2-one. The latter substance was then elaborated to **46** by removal of the Cbz group according to method B and final urea formation with *m*-methylphenyl isocyanate following the procedure of method A: mp 172 °C dec; R_f = 0.17 ($CHCl_3$/MeOH, 9:1); ^1H NMR (DMSO-d_6) δ 2.15 (s, 3H), 2.25 (s, 3H), 5.05 (d, 2H), 5.35 (d, 1H, C*H*NH), 5.36 (d, 1H), 6.75 (d, 1H), 7.05–7.6 (m, 11H), 7.68 (t, 1H), 7.80 (d, 1H), 9.05 (s, 1H); FAB MS 480 (M^+ + H). Anal. ($C_{27}H_{25}N_7O_2$·0.3$CHCl_3$·0.85 MeOH) C, H, N.

1,3-Dihydro-5-phenyl-3(*S*)-{[[[(*S*)-(−)-*sec*-phenethyl]oxy]-carbonyl]amino}-2*H*-1,4-benzodiazepin-2-one (VIa) and 1,3-dihydro-5-phenyl-3-(*R*)-{[[[(*S*)-(−)-*sec*-phenethyl]oxy]carbonyl]amino}-2*H*-1,4-benzodiazepin-2-one (VIb). To a solution of **IIa** (647 mg, 2.57 mmol) in 20 mL of THF was added 459 mg (2.83 mmol) of carbonyldiimidazole in one portion. The homogeneous reaction mixture was allowed to stand at room temperature overnight, whereupon it was concentrated to half its volume and treated with 1.06 mL (15.51 mmol) of (*S*)-(−)-*sec*-phenethyl alcohol. The resulting mixture was then heated to reflux for 75 h. The reaction mixture was cooled and concentrated, and the residual material was flash chromatographed on silica gel (28% EtOAc/hexane to 40% EtOAc/hexane gradient) to give 350 mg each of diastereomer **VIa** and **VIb** (>70% enriched). Two recrystallizations of **VIa** from ethyl acetate afforded 50 mg of diastereomerically pure product: mp 126–127 °C; ^1H NMR ($CDCl_3$) δ 1.57 (d, 3H), 5.35 (d, 1H, C*H*NH), 5.82 (q, 1H), 6.51 (d, 1H, CHN*H*), 7.1–7.55 (m, 14H), 7.84 (br s, 1H); FAB MS 400 (M^+ + H). Additional processing of **VIb** via PLC chromatography (hexane–ethyl acetate, 65:35, v/v, multiple elutions) gave 170 mg of homogeneous product: ^1H NMR ($CDCl_3$) δ 1.58 (d, 3H), 5.31 (d, 1H, C*H*NH), 5.80 (q, 1H), 6.60 (d, 1H, CHN*H*), 7.1–7.57 (m, 14H), 8.19 (br s, 1H); FAB MS 400 (M^+ + H).

***N,N*-Tetramethylene-3-(*S*)-{[[[(*S*)-(−)-*sec*-phenethyl]oxy]-carbonyl]amino}-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetamide (VIIa).** The carbamate **VIa** (152 mg, 0.38 mmol) was metalated at 0 °C for 1 h with a suspension of 17.5 mg of sodium hydride (0.437 mmol, 50% in oil) in 5 mL of dry DMF. *N*-(2-Iodoacetyl)pyrrolidine (109 mg, 0.456 mmol) in 1 mL of DMF was then added, and stirring was continued at 0 °C for 1 h more. The solvent was removed under reduced pressure, and the residual material was purified via PLC chromatography (ethyl acetate–hexane, 3:2) to give 156 mg (80%) of **VIIa** as a single isomer: ^1H NMR ($CDCl_3$) δ 1.55 (d, 3H), 1.85 (m, 2H), 1.98 (m, 2H), 3.40 (m, 2H), 3.55 (m, 2H), 4.40 (d, 1H), 4.71 (d, 1H), 5.43 (d, 1H, C*H*NH), 5.70 (q, 1H), 6.65 (d, 1H, CHN*H*), 7.25–7.60 (m, 14H); FAB MS 511 (M^+ + H).

***N,N*-Tetramethylene-3-(*R*)-{[[[(*S*)-(−)-*sec*-phenethyl]oxy]-carbonyl]amino}-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetamide (VIIb).** The carbamate **VIb** (161 mg, 0.403 mmol) was converted to **VIIb** using identical reaction conditions to those described for the preparation of **VIIa**: ^1H NMR ($CDCl_3$) δ 1.58 (d, 3H), 1.82 (m, 2H), 1.95 (m, 2H), 3.39 (m, 2H), 3.52 (m, 2H), 4.41 (d, 1H), 4.69 (d, 1H), 5.39 (d, 1H, C*H*NH), 5.78 (q, 1H), 6.70 (d, 1H, CHN*H*), 7.2–7.65 (m, 14H); FAB MS 511 (M^+ + H).

***N,N*-Tetramethylene-3-(*S*)-{[((4-chlorophenyl)amino)-carbonyl]amino}-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetamide (26).** The carbamate **VIIa** (72 mg, 0.141 mmol) was dissolved in 3 mL of ice-cold methylene chloride and treated with a continuous stream of HBr gas for 3 min. The reaction mixture was protected from moisture and stirred at 0 °C for 15 min more. All volatiles were removed under reduced pressure, and the residual HBr salt was azeotropically dried with toluene (2 cycles). This material (56 mg, 0.126 mmol) was dissolved in 5 mL of warm THF, cooled to 0 °C, and treated in succession with 17.6 μL (0.126 mmol) of triethylamine and 19.3 mg (0.126 mmol) of *p*-chlorophenyl isocyanate. The reaction mixture was filtered after 10 min, and the filtrate was concentrated in vacuo. PLC chromatography (chloroform–methanol, 9:1) of the residue, followed by trituration with ethyl acetate–petroleum ether, afforded 55 mg (84%) of the analytical product: mp 192 °C; $[\alpha]_D$ = −68.2° (*c* = 0.11, $CHCl_3$); R_f = 0.20 ($CHCl_3$/CH_3OH/concentrated NH_4OH, 95:5:0.5); ^1H NMR (DMSO-d_6) δ 1.76 (ddd, 2H), 1.89 (ddd, 2H), 3.27 (t, 2H), 3.49 (m, 2H), 4.74 (s, 2H), 5.32 (d, 1H, C*H*NH), 7.25–7.6 (m, 13H), 7.69 (t, 1H), 9.21 (s, 1H); FAB MS 516 (M^+ + H). Anal. ($C_{28}H_{26}ClN_5O_3$·0.1$CHCl_3$) C, H, N.

***N,N*-Tetramethylene-3-(*R*)-{[((4-chlorophenyl)amino)-carbonyl]amino}-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetamide (27).** The carbamate **VIIb** (198 mg, 0.38 mmol) was dissolved in 20 mL of methanol containing 90% formic acid (4.5 % by volume). This solution was pipetted into a suspension of 10% palladium/carbon catalyst (51 mg) in 20 mL of the above solvent mixture. The resulting reaction mixture was stirred at 40 °C under nitrogen for 12 h. The reaction mixture was filtered through Celite, and the filtercake was washed with methanol/formic acid. The combined filtrate and washings were concentrated in vacuo, and the residue was azeotropically dried with toluene to give 99 mg (65%) of **VIIb** as the formate salt. This material was carried on in a manner identical to the preparation of **26** affording **27** in 70% yield after trituration with ethyl acetate/petroleum ether: mp 258 °C; $[\alpha]_D$ = +98.8° (*c* = 0.04, $CHCl_3$). Anal. ($C_{28}H_{26}ClN_5O_3$·0.7H_2O·0.05C_4H_8O) C, H, N.

(*R,S*)-*N*-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-phenylurea (52). The amine **VIII** (102 mg, 0.35 mol) was combined with phenyl isocyanate (41 μL, 0.35 mmole) in 3 mL of dry THF at room temperature. Within 10 min a white precipitate was deposited. The reaction mixture was filtered after 1 h to yield 87 mg (60%) of the product in analytically pure form: mp 260–261 °C; ^1H NMR (DMSO-d_6) δ 3.41 (s, 3H), 5.26 (d, 1H, C*H*NH), 6.93 (t, 1H), 7.25 (t, 1H), 7.35–7.55 (m, 11H), 7.69 (d, 1H), 7.75 (ddd, 1H), 9.1 (s, 1H); MS *m/e* 402 (M^+), 357, 256, 216, 174, 147 (100). Anal. ($C_{23}H_{20}N_4O_2$) C, H, N.

1,3-Dihydro-5-phenyl-3(*R,S*)-[[(4-nitrophenoxy)carbonyl]amino]-2*H*-1,4-benzodiazepin-2-one (IX). To a magnetically stirred solution of 75 mL of dry THF containing 4.4 mL (31.7 mmol) of triethylamine was added the amine **VIII** (8 g, 30.15 mmol) at 0 °C. 4-Nitrophenyl chloroformate (6.39 g, 31.7 mmol) in 25 mL of THF was then added over a 5-min period. Stirring was continued for 15 min more, and the reaction mixture was filtered. Rotoevaporation of the filtrate afforded a semisolid which was flash chromatographed (4% Et_2O–CH_2Cl_2) to give 11.82 g (91%) of **IX** as an off-white solid: mp 91–93 °C; ^1H NMR ($CDCl_3$) 3.52 (s, 3H), 5.35 (d, 1H, C*H*NH), 6.81 (d, 1H), 7.12 (d, 1H), 7.27 (t, 1H), 7.4 (m, 4H), 7.45 (ddd, 1H), 7.61 (d, 2H), 7.62 (t, 1H), 8.09 (d, 1H), 8.25 (d, 2H); FAB MS 431 (M^+ + H). Anal. ($C_{23}H_{18}N_4O_5$) C, H, N.

1,3-Dihydro-5-phenyl-3(*R*)-[[(4-nitrophenoxy)carbonyl]amino]-2*H*-1,4-benzodiazepin-2-one (IXa): mp 84–87 °C; $[\alpha]_D$ = +35.5° (*c* = 0.6, $CHCl_3$). Anal. ($C_{23}H_{18}N_4O_5 \cdot 1.2H_2O$) C, H, N.

(*R*)-*N*-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3,4-dimethylphenyl)urea (83). Method D. A solution of THF (6 mL) containing 156 mg (0.362 mmole) of **IXa** and 44.6 mg (0.398 mol) of 3,4-dimethylaniline was treated with 52 μL (0.37 mmol) of triethylamine at ambient temperature. An immediate yellow coloration of the reaction mixture ensued (4-nitrophenoxide). The reaction mixture was stirred for 2 h and then concentrated to dryness under reduced pressure. Plug filtration (SiO_2) of the crude product to remove 4-nitrophenol gave a solid which was recrystallized from methanol (137 mg, 90%): mp 165–167 °C; ^1H NMR (DMSO-d_6) δ 2.12 (s, 3H), 2.17 (s, 3H), 3.4 (s, 3H), 5.24 (d, 1H, C*H*NH), 6.98 (d, 1H), 7.09 (d, 1H), 7.18 (s, 1H), 7.3–7.55 (m, 8H), 7.68 (d, 1H), 7.72 (t, 1H), 8.85 (br s, 1H); FAB MS 413 ($M^+ + H$). Anal. ($C_{25}H_{24}N_4O_2$) C, H, N.

(*R*)-*N*-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3-styryl)urea (88). Method E. A solution of 3-aminostyrene (730 mg, 6.13 mmol) in 40 mL of THF was cooled to 0 °C and mixed with 606 mg (2.04 mmol) of triphosgene. To this suspension was added 1.71 mL (12.3 mmol) of triethylamine in approximately three equal portions over 5 min (pH >8, moist pH paper). The resulting thick suspension was stirred for 5 min more at 0 °C and 5 min at room temperature and then was recooled to 0 °C. A solution of the amine **VIIIa** (1.46 g, 5.52 mmole) in 15 mL of THF was added, and the reaction temperature was raised to 23 °C. After 30 min the reaction mixture was diluted with 100 mL of ethyl acetate and was washed with 10% citric acid solution and brine. The dried (Na_2SO_4) organic extracts were concentrated and flash chromatographed (ethyl acetate–hexane) to yield 1.867 g (82%) of **88**: mp 212–214 °C; ^1H NMR ($CDCl_3$) δ 3.41 (s, 3H), 5.2 (d, 1H, C*H*NH), 5.6 (d, 1H), 5.65 (d, 1H), 6.61 (dd, 1H), 7.05–7.75 (m, 15H); FAB MS 519 ($M^+ + H$ + thioglycerol matrix), 411 ($M^+ + H$). Anal. ($C_{25}H_{22}N_4O_2 \cdot 0.3H_2O \cdot 0.05EtOAc$) C, H, N.

1,3-Dihydro-5-(2-pyridyl)-3-(*R,S*)-[(benzyloxycarbonyl)amino]-2*H*-1,4-benzodiazepin-2-one (XI). α-[(*tert*-Butyloxycarbonyl)amino]-N^α-(benzyloxycarbonyl)glycine (2.8 g, 8.6 mmole) was combined with 0.96 mL (8.7 mmol) of *N*-methylmorpholine in 85 mL of methylene chloride. The solution was cooled to 0 °C, and 1.12 mL (8.7 mmol) of isobutyl chloroformate was added dropwise. After 0.5 h, 2-(2'-aminobenzoyl)pyridine (1.6 g, 8.6 mmol) was added in one portion. The resulting reaction mixture was stirred at 0 °C for 0.5 h and then at ambient temperature for 4 h more. The reaction mixture was concentrated under reduced pressure, and the residue was flash chromatographed on silica gel (methylene chloride elution, then methylene chloride–ethyl ether gradient, 5–20%) to yield 2.6 g (60%) of 2-[*N*-[α-[(*tert*-butyloxycarbonyl)amino]-N^α-(benzyloxycarbonyl)glycinyl]-2'-aminobenzoyl]pyridine, **X**.

An ice-cold solution of 50 mL of ethyl acetate containing 1.9 g (3.7 mmol) of **X** was saturated with HCl gas and subsequently stirred for 10 min. A continuous stream of nitrogen was then passed through the reaction medium to remove excess HCl. The reaction mixture was concentrated *in vacuo*, and the residue was treated with saturated sodium carbonate solution. The alkaline solution was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue thus obtained was immediately dissolved in 30 mL of glacial acetic, treated with 1.7 g (22.6 mmol) of ammonium acetate, and stirred overnight at ambient temperature. Filtration of the reaction mixture, followed by rotoevaporation of the filtrate and extractive workup with ethyl acetate, gave 1.27 g (87%) of the title compound **XI**: mp 214–215 °C; R_f = 0.29 (5% CH_3OH/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 5.17 (AB q, 2H), 5.39 (d, 1H, C*H*NH), 6.66 (d, 1H, CHN*H*CO), 7.02 (d, 1H), 7.21 (t, 1H), 7.30–7.42 (m, 7H), 7.48 (ddd, 1H), 7.83 (ddd, 1H), 8.09 (d, 1H), 8.4 (br s, 1H), 8.61 (d, 1H); FAB MS 387 ($M^+ + H$). Anal. ($C_{22}H_{18}N_4O_3$) C, H, N.

***N,N*-Diethyl-3-{[(3-Methylphenyl)amino)carbonyl]amino}-2,3-dihydro-2-oxo-5-(2-pyridyl)-1*H*-1,4-benzodiazepine-1-acetamide (114).** To a magnetically stirred suspension of sodium hydride (37.3 mg, 0.77 mmol, 50% suspension in oil) in 10 mL of degassed DMF was added a solution of **XI** (300 mg, 0.77 mmol) in 5 mL of degassed DMF at 0 °C. After 1 h, 234 mg (0.97 mmol) of *N,N*-diethyliodoacetamide was added. The reaction mixture was stirred overnight, during which time it was warmed from 0 °C to room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The crude product was flash chromatographed on silica gel (15% acetone/methylene chloride) to give 220 mg (56%) of the 1,3-dihydro-1-(*N,N*-diethylacetamido)-5-(2-pyridyl)-3(*R,S*)-[(benzyloxycarbonyl)amino]-2*H*-1,4-benzodiazepin-2-one derivative of **XII** which was used directly in the next step.

The latter material (220 mg, 0.44 mmol) was dissolved in 15 mL of dry methylene chloride containing 0.5 mL of glacial acetic acid, cooled to 0 °C, and treated with a continuous stream of HBr gas for 30 min. Nitrogen gas was passed through the reaction mixture to displace excess HBr, and the reaction mixture was concentrated *in vacuo*. The residual semisolid was dissolved in ethyl acetate (100 mL) and treated with 1 N sodium hydroxide solution. The aqueous phase was extracted with ethyl acetate, and the combined extracts were dried and concentrated to give 161 mg (100%) of **XII**. This material (100 mg, 0.27 mmol) was dissolved in 110 mL of ethyl acetate and treated with 38.8 mL (0.30 mmol) of *m*-tolyl isocyanate at 25 °C. The clear solution was stirred for 15 min and concentrated to approximately 1-mL volume. Ethyl ether was added to precipitate **114** which was obtained in analytical form (101 mg, 74%) after further washing with ether: mp 201–207 °C; R_f = 0.49 (CH_2Cl_2/CH_3OH/concentrated NH_4OH, 80:10:1 v/v); ^1H NMR ($CDCl_3$) δ 1.16 (t, 3H), 1.22 (t, 3H), 2.31 (s, 3H), 3.31 (m, 2H, $CH_2CON(CH_2CH_3)_2$), 3.45 (m, 2H, $CH_2CON(CH_2CH_3)_2$), 4.27 (d, 1H, CH_2CONEt_2), 4.87 (d, 1H, CH_2CONEt_2), 5.70 (d, 1H, C*H*NH), 6.60 (br s, 1H), 6.77 (d, 1H), 6.87 (d, 1H), 7.15 (m, 2H), 7.25 (m, 2H), 7.35 (m, 2H), 7.45 (d, 1H), 7.55 (ddd, 1H), 7.80 (ddd, 1H), 8.19 (d, 1H), 8.60 (d, 1H); MS *m/e* 498 (M^+), 365 (M^+ – *m*-tolyl isocyanate), 265, 195, 133, (100). Anal. ($C_{28}H_{30}N_6O_3 \cdot 0.15Et_2O \cdot 0.5EtOAc$) C, H, N.

Modified Radioreceptor Binding Protocol. Assays were conducted in a modified Hepes Krebs' buffer, pH 6.5, containing 20 mM Hepes, 1 mM EGTA, 5 mM $MgCl_2$, and 150 mM NaCl. The pancreas assay also contained 0.25 mg/mL bacitracin, 0.1 mg/mL soybean trypsin inhibitor, and 2 mg/mL BSA. Tissue was resuspended at 1 g (original wet weight) to 2000 mL (pancreas) and 120 mL (brain). Following a 90-min incubation, samples were filtered over GF/C filters and washed with ice-cold 100 mM NaCl. In all cases, the IC_{50} values shown are the means of triplicate determinations.

Oral Bioavailability Protocol. Plasma from rats dosed with 2.5 mg/kg of a test compound was collected for HPLC analysis. The plasma samples were prepared by solid-phase extraction with 3-mL cyano (CN) extraction cartridges (Baker 7021). The residues were reconstituted in methanol, centrifuged, and chromatographically separated on a Whatman Partisil 5 ODS-3 RAC II column (0.1% H_3PO_4 in water and acetonitrile, 55:45, v/v elution). The peak height ratios were calculated and unknown sample concentrations were determined from a least-squares linear regression analysis of the standard's (compound **52**) peak height ratios versus a concentration curve. The analytical procedure was linear over a 2-4000 ng/mL range (0.5-mL assay). The variability of quality control samples from day to day was 3.7%.

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