Articles

Synthesis and SAR of New 5-Phenyl-3-ureido-1,5-benzodiazepines as Cholecystokinin-B Receptor Antagonists

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A series of 5-phenyl-3-ureidobenzodiazepine-2,4-diones was synthesized and evaluated as cholecystokinin-B (CCK-B) receptor antagonists. Structure−activity relationship (SAR) studies revealed the importance of the N-1 substituent for potent and selective CCK-B affinity. Addition of substituents at the urea side chain provided in some cases more potent compounds. Moreover the introduction of bulky substituents such as adamantylmethyl at N-1 and resolution of the racemic ureas resulted in our lead compound GV150013.

Introduction

Cholecystokinin (CCK) is a gastrointestinal peptide hormone of 33 amino acids that was originally isolated from porcine gut.[1] It is also found in high concentrations in the brain, mainly as the C-terminal octapeptide,[2,3] usually sulfated on tyrosine 7 (CCK-8S). CCK exhibits many of the characteristics of a neurotransmitter: it is synthesized in neurons, it is stored in synaptic vesicles, it is metabolized in the brain, it is released upon depolarization, and it has specific binding sites associated with nerve terminals containing CCK.[4] Thus, CCK can be considered to belong to a class of peptides that act both as gut hormones and as central neurotransmitters. CCK interacts with at least two types of receptors.[5] These subtypes have been designated CCK-A and CCK-B. The former is located predominantly in the periphery, and the latter is found in high abundance in the brain. The gastrin receptor of the stomach shares similarities with the CCK-B receptor but can be pharmacologically distinguished from it.[6,7] The classification of CCK receptors into two subtypes is supported by the use of nonpeptidic, selective competitive antagonists, like L-364,718 ((*S*)-devazepide)[8,9] and the peptoid PD-134308[10] (CI-988) for CCK-A and CCK-B receptors, respectively (Figure 1). The regional distribution of the two receptors in the brain together with studies with selective agonists and antagonists in different animal models have suggested possible therapeutic targets for drugs acting through CCK receptors. These include

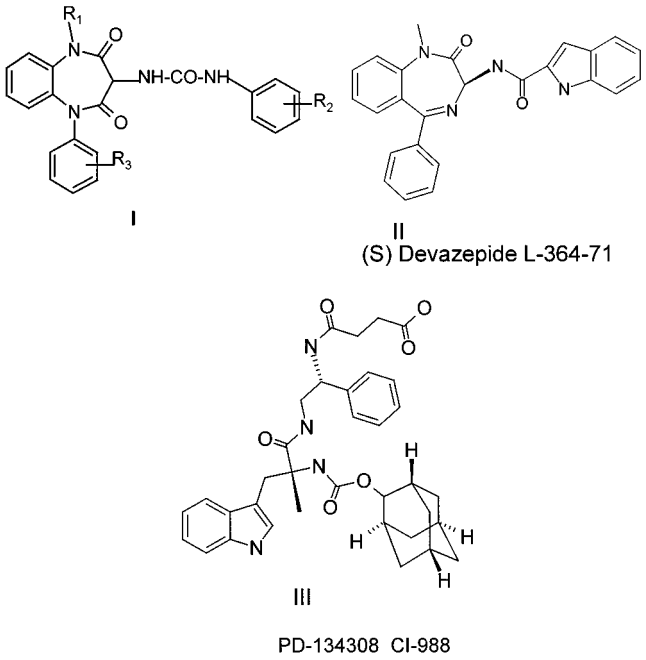

Figure 1. Chemical structure of 3-(arylaminocarbonyl)amino- or 3-(aryloxycarbonyl)amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**I**), devazepide (**II**), and PD-134308 (**III**).

cognitive processes, emotional states such as anxiety[10] and panic, motivation such as drug-seeking behavior, nociception,[11] and sleep disorders.[12] CCK-B antagonists have been developed from numerous structural classes.[13] One of the most throughly investigated is the benzodiazepine family, represented by the potent and selective L-365,260.

As part of our research for new anxiolytic compounds acting as potent and selective CCK-B antagonists and devoid of side effects which are typical of marketed

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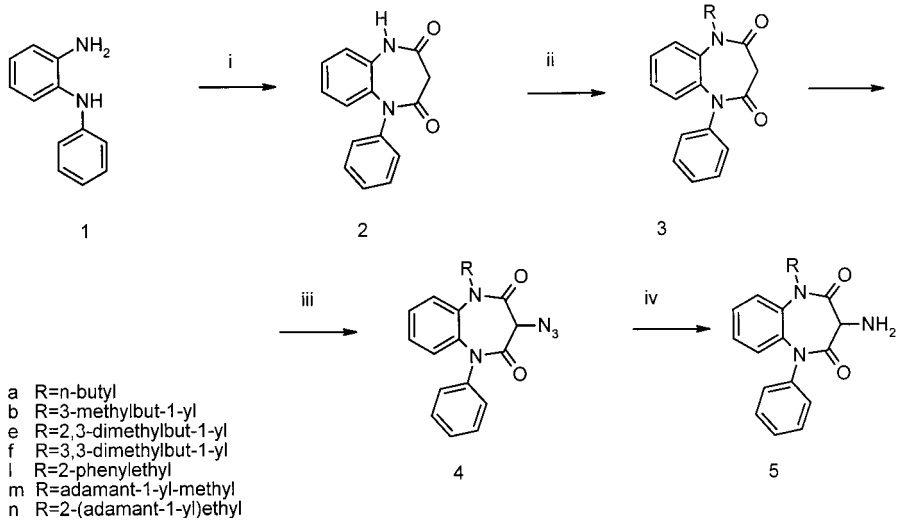
Scheme 1[a]



[a] Reagents and conditions: (i) ref 18; (ii) NaH, RX, DMF, rt, 20 h; (iii) ^{t}BuOK, $ArSO_2N_2$, THF, −78−0 °C, 24 h; (iv) H_2/Pd, C, $CaCO_3$, AcOEt, EtOH, 1 atm, rt, 4 h.

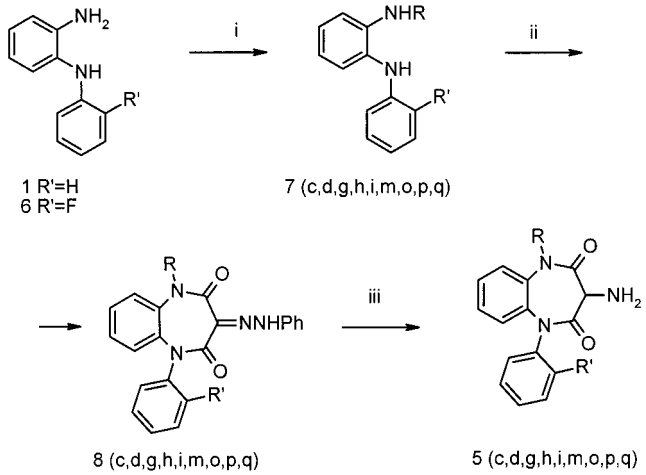
drugs, we investigated a novel class of 1,5-benzodiazepine-2,4-diones, which was considered an attractive template in view of combining the high flexibility in the substitution pattern and the potentially straightforward synthesis and high-yielding processes to be applied for their preparation.

Chemistry

Initially, compounds bearing an aryl substituent at the N-5 position and either 3-(arylaminocarbonyl)amino or 3-(aryloxycarbonyl)amino at the C-3 position (Figure 1, structure **I**, X = NH) were prepared, and the nature of the substituent at N-1 position was particularly explored.[14,15] The synthesis of both classes of compounds has been accomplished according to the same procedure, and here we report detailed results only on ureido derivatives (Figure 1, X = NH). The structures of 3-ureido-1,5-benzodiazepines which comprise this report are presented in Table 1. The compounds collated in Table 1 were prepared according to the general processes outlined in Schemes 1−3, the key precursor of the ureidic bond being the free amine **5** depicted in Figure 2, which may be easily transformed into the target compounds **I** of Figure 1. It is worth noting that above-mentioned compounds have a stereogenic center at C-3, and its resolution may be crucial in view of the pharmacological profile of the pure enantiomers (see below). Since the reaction outlined in Scheme 3 is unlikely to cause racemization at C-3, it is clear that it would be possible to obtain the enantiomerically pure ureas after separation of the corresponding amines **5**, thus highlighting the strategic importance of such a key intermediate. The synthesis of the key intermediate **5** follows procedures disclosed in earlier reports.[14−16] Representative reaction conditions are provided in the Experimental Section describing the preparation of compounds represented in Schemes 1−3.

For the synthesis of compounds **13**, **14**, **24**, **25**, **31**, **32**, **47** and **54**−**63**, pure enantiomers of the required intermediate reported in Figure 2 were obtained in chirally homogeneous form according to the procedure summarized in Scheme 4.

Scheme 2[a]

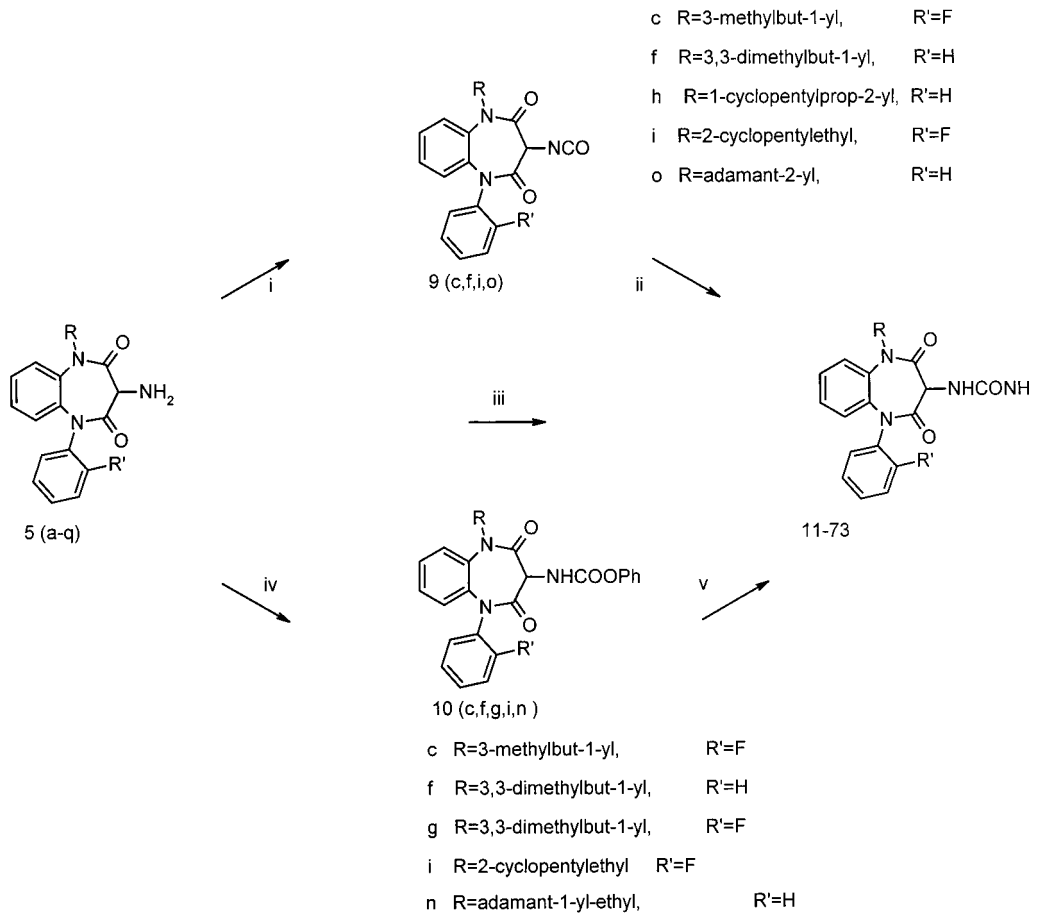


c R=3-methylbut-1-yl, R'=F
d R=1,3-dimethylbut-1-yl, R'=H
g R=3,3-dimethylbut-1-yl, R'=F
h R=1-cyclopentylprop-2-yl, R'=H
i R=2-cyclopentylethyl, R'=F
m R=1-adamant-1-yl-methyl, R'=H
o R=adamant-2-yl, R'=H
p R=bicyclo[2.2.1]-2-heptyl, R'=H
q R=2-Adamant-2-yl-methyl, R'=H

[a] Reagents and conditions: (i) RBr, NaH (method A) or RCHO, $NaCNBH_3$ (method B_1) or R_2CO, toluene, molecular sieves, 120 °C, 6 h then $NaBH_4$, EtOH, rt, 30 min (method B_2); (ii) PhNH-$CH(COCl)_2$, THF, 50 °C, 3 h; (iii) Zn/AcOH, rt, 6 h or H_2, Pd/C, HCl, AcOEt, H_2O, atm, rt, 4 h.

Two main synthetic approaches were used for the preparation of free amines **5**. A first procedure (Scheme 1) considered as a common intermediate the 2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine **(2)**, obtained using known procedure from commercially available phenylenediamine **1**.[17] Alkylation at the N-1 position of the benzodiazepine nucleus using either an alkyl bromide or an alkyl mesylate gave compounds **3**

Scheme 3[a]



[a] Reagents and conditions: (i) $COCl_2$ in toluene solution, CH_2Cl_2, rt, 4 h; (ii) $ArNH_2$, CH_2Cl_2, CH_3CN, rt, 7 h; (iii) ArNCO, CH_2Cl_2, rt, 1 h; (iv) PhOCOCl, Py, CH_2Cl_2, rt, 30 min; (v) $ArNH_2$, DMF, 160 °C, 2 h.

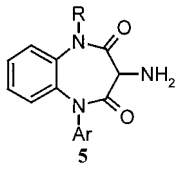


Figure 2. 3-Amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine.

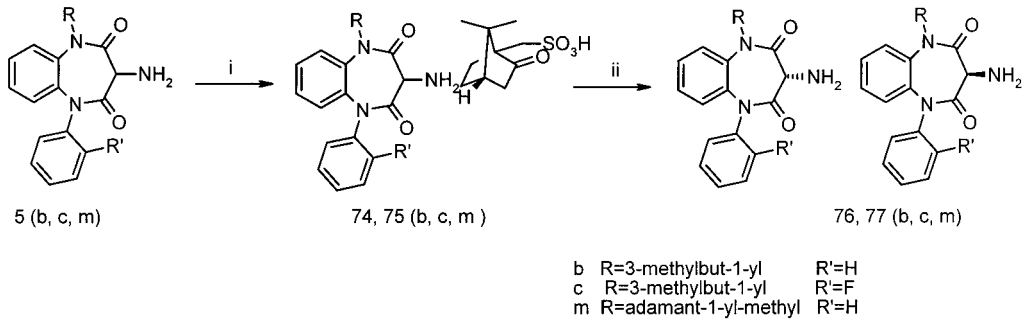
in moderate to high yield, depending on the steric hindrance of the alkyl group. Subsequently an azido group was introduced at the C-3 position generally using 2,4,6-triisopropylbenzenesulfonyl azide in the presence of a base (e.g. potassium *tert*-butoxide). The azido group in compounds **4** was then hydrogenated to the corresponding amines of general formula **5** by using palladium on calcium carbonate as catalyst.

The alkylation of the intermediate **2** represents the limiting step of the above-mentioned route, and yields may be very low according to the steric hindrance of the alkylating agent. Moreover, the synthesis of benzodiazepines substituted either at the N-5 phenyl (e.g. **15**, **19**, **21**) or at the fused aromatic ring[16] generally required a noncommercially available substituted phenylenediamine as starting materials. Therefore, an alternative route was set up as reported in Scheme 2. The starting phenylenediamines **1** and **6** were generally prepared by reaction of 2-fluoronitrobenzene or substituted 2-fluoronitrobenzene with either aniline or 2-fluoroaniline in the presence of potassium fluoride and subsequent reduction of the nitro group.[16] The resulting amines were alkylated generally by using an alkyl bromide in the presence of sodium hydride to obtain the intermediates **7**. When bulky groups had to be introduced, the intermediate **7** was conveniently obtained by reductive amination of either aldehydes or ketones (**7m,p**). The condensation of **7** with phenylhydrazonomalonyl dichloride[18] followed by reduction with zinc and acetic acid led to the 3-amino-substituted benzodiazepines **5**.

The final ureido derivatives **I** listed in Table 1 were made available by well-known methods, outlined in Scheme 3. The reaction with aryl isocyanate is obviously the most convenient, but the other routes involving either the synthesis of 3-isocyanobenzodiazepines **9** by reaction with phosgene or the synthesis of carbamate **10** by reaction with phenyl chloroformate[19] have proven useful particularly when the required substituted aryl isocyanates were not commercially available. Although modulation of the binding affinity was achieved by introducing appropriate substituents at the aromatic rings, the most remarkable increase in affinity and CCK-B receptor selectivity was found with the resolution of the stereogenic center at C-3 of the benzodiazepine ring.

As far as the resolution into enantiomers is concerned, preparative HPLC performed on final ureas was initially used, but it had to be limited to small-scale preparations. Therefore, a more general and effective chemical method was sought, and attention was focused

Scheme 4[a]



[a] Reagents and conditions: (i) (1*R*)-(−)-10-camphorsulfonic acid, EtOAc; (ii) 5% NH_4OH, $CHCl_3$. Experimental procedures described in ref 14.

on the enantiomeric separation of the corresponding amine precursors, particularly taking into account that their transformation to the target ureas generally involves nonracemizing conditions. Several known resolution methods could in theory be applied to our class. Among them, the most common is the formation and preferential crystallization of diastereomeric salts with chiral acids (e.g. camphorsulfonic acid, Scheme 4).[20] The use of covalent diastereomeric derivatives (e.g. amides) is generally precluded by the strong conditions required for their cleavage to obtain the resolved amines, but recently the resolution of 3-amino-1,4-benzodiazepines was achieved by means of the preparation and separation of diastereomeric phenylalanyl amides[21−23] or carbamates.[24] This procedure, which is based upon the reaction of the racemic amine with N-Boc-protected phenylalanine, followed by separation of the two diastereomeric amides and subsequent Edman degradation, was also applied to our series, and the desired enantiomers were obtained with excellent enantiomeric excess. However, the total yield of the process was quite low due to a difficult chromatographic separation of the two diastereomers and the low conversion during the Edman degradation step. Therefore, we developed a new method based on the resolution of phenylglycine derivatives.[25,26] Accordingly, the racemic amine is reacted with a chiral auxiliary, namely the tosyl derivative of (*S*)-(+)-methyl mandelate, followed by the chromatographic separation of the two diastereomers formed and the subsequent hydrogenation of the separated compounds to give the free amines with good enantiomeric excess. As anticipated, the enantiomerically pure amines **5** were converted into the target ureas without observing any racemization. As far as the absolute configuration of these compounds is concerned, X-ray analysis of single crystals of the 4-bromophenyl compound **56** was performed and coupled to CD measurements of both enantiomers among a series of derivatives; as a result, the (*R*)-configuration for the (+)-enantiomer was unambiguously confirmed.

Biology

All the compounds synthesized were tested in vitro according to slighty modified methods to determine their affinity for CCK-A and CCK-B[27,28] receptor subtypes. The affinity and B/A selectivity of 1,5-benzodiazepines with different substitutions have been determined by radioligand binding studies using cerebral cortex membranes from guinea-pig and rat (CCK-B receptors) as well as rat pancreatic membranes (CCK-A receptors) and are listed in Table 2.

Furthermore, for a selected group of compounds, species selectivity was determined for CCK-B receptors using membranes from guinea-pig and rat as well as HeLa transfected human cortical CCK-B receptors. The results for the best compound GV150013 (**24**) and reference antagonists are discussed in the next section and summarized in Table 3. The more interesting compounds were also evaluated in vivo to establish their anxiolytic activity.[29] Finally, some compounds have been evaluated in comparison with diazepam for potential side effects such as tolerance and withdrawal.

Results and Discussion

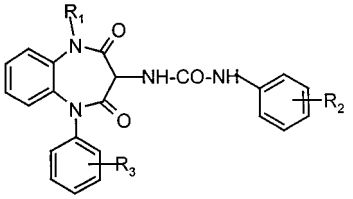
Considering the general formula **I** of Figure 1 a high flexibility toward the substitution pattern is evident. At first, we carried out a wide exploration to understand which kind of substitution would be more critical to our objective. After an initial evaluation, we restricted our interest in compounds bearing both an aryl substituent at the N-5 position and an alkyl chain at the N-1 position, and two main subclasses of derivatives were selected, that is C-3 ureas and C-3 carbamates. Here the discussion is dedicated to the former, while carbamates have been discussed in detail elsewhere.[30,31] In view of optimizing the in vitro profile of a first set of derivatives, we focused our attention on the nature of the substituent at the N-1 position and a quantitative structure−activity (QSAR) study was performed on a series of 21 N-1 alkyl derivatives. A model was derived using PLS analysis implemented in program GOLPE.[32] After variable selection, a 4-component model was obtained that explains 84% of the activity variance. The model was transformed into a pseudo-MLR (multiple linear regression) equation where a single pseudo-coefficient multiplies each independent variable. These coefficients express the effect of each single *X*-parameter on the dependent variable and can be useful to interpret the whole model:

$$p\mathit{K}_i(\mathrm{B}) = 0.49p_i - 0.13p_i^2 - 0.44\mathrm{MR} - 0.20\mathrm{MR}^2 + 0.39\mathrm{Sb} - 0.67D_1 + 7.15$$

$$\mathrm{LV} = 4,\ R^2 = 0.84,\ s = 0.21,\ n = 21$$

All the parameters in the equation are referred to the substituents at N-1: $p\mathit{K}_i$(B) is the affinity for the CCK-B receptor subtype; p_i is the calculated lipophilicity;[33] MR

Table 1. 1-Alkyl-5-aryl-3-ureido-1,5-benzodiazepine-2,4-dione

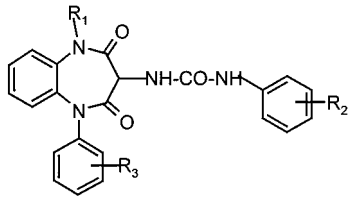


compd	R_1	R_2	R_3	stereo	synth method (Scheme 3)
11	butyl	H	H	rac	iii
12	3-methylbut-1-yl	H	H	rac	iii
13	3-methylbut-1-yl	H	H	+	iii
14	3-methylbut-1-yl	H	H	−	iii
15	3-methylbut-1-yl	H	F	rac	iii
16	1,3-dimethylbut-1-yl	H	H	rac	iii
17	2,3-dimethylbut-1-yl	H	H	rac	iii
18	3,3-dimethylbut-1-yl	H	H	rac	iii
19	3,3-dimethylbut-1-yl	H	F	rac	iii
20	1-cyclopentylprop-2-yl	H	H	rac	iii
21	2-cyclopentylethyl	H	F	rac	iii
22	2-phenylethyl	H	H	rac	iii
23	adamant-1-ylmethyl	H	H	rac	iii
24 (GV150013)	adamant-1-ylmethyl	H	H	+	iii
25	adamant-1-ylmethyl	H	H	−	iii
26	2-(adamant-1-yl)ethyl	H	H	rac	iii
27	adamant-2-yl	H	H	rac	iii
28	bicyclo[2.2.1]-2-heptyl	H	H	rac	iii
29	adamant-2-ylmethyl	H	H	rac	iii
30	3-methylbut-1-yl	3-*N*,*N*-dimethylamino	F	rac	iii, v
31	3-methylbut-1-yl	3-*N*,*N*-dimethylamino	F	+	iii
32	3-methylbut-1-yl	3-*N*,*N*-dimethylamino	F	−	iii
33	3-methylbut-1-yl	3-methylthio	F	rac	ii
34	3,3-dimethylbut-1-yl	3-*N*,*N*-dimethylamino	H	rac	v
35	3,3-dimethylbut-1-yl	3-methylthio	H	rac	v
36	3,3-dimethylbut-1-yl	3-cyano	H	rac	ii
37	3,3-dimethylbut-1-yl	3-(tetrazol-5-yl)	H	rac	ii
38	3,3-dimethylbut-1-yl	3-[2-(2,2-dimethylethyl)tetrazol-5-yl]	H	rac	ii
39	3,3-dimethylbut-1-yl	3-trifluoromethoxy	H	rac	ii
40	3,3-dimethylbut-1-yl	3-methylthio	F	rac	ii
41	3,3-dimethylbut-1-yl	3-*N*,*N*-dimethylamino	F	rac	v
42	2-cyclopentylprop-2-yl	3-(tetrazol-5-yl)	H	rac	ii
43	2-cyclopentylethyl	3-*N*,*N*-dimethylamino	F	rac	ii
44	2-cyclopentylethyl	4-*N*,*N*-dimethylamino	F	rac	ii
45	2-cyclopentylethyl	3-methylthio	F	rac	ii
46	2-cyclopentylethyl	3-(tetrazol-5-yl)	F	rac	ii
47	adamant-1-ylmethyl	3-hydroxy	H	+	iii
48	adamant-1-ylmethyl	3-methyl	H	rac	iii
49	adamant-1-ylmethyl	3-nitro	H	rac	iii
50	adamant-1-ylmethyl	3-bromo	H	rac	iii
51	adamant-1-ylmethyl	3-ethoxycarbonyl	H	rac	iii
52	adamant-1-ylmethyl	3-carboxy	H	rac	iii
53	adamant-1-ylmethyl	3-*N*,*N*-dimethylamino	H	rac	iii
54	adamant-1-ylmethyl	3-hydroxymethyl	H	+	iii
55	adamant-1-ylmethyl	3-(morpholin-4-yl)methyl	H	+	iii
56	adamant-1-ylmethyl	4-bromo	H	+	iii
57	adamant-1-ylmethyl	3-bromo	H	+	iii
58	adamant-1-ylmethyl	4-(3-ethoxycarbonylpropyl)oxy	H	+	iii
59	adamant-1-ylmethyl	4-(3-carboxypropyl)oxy	H	+	iii
60	adamant-1-ylmethyl	4-hydroxy	H	+	iii
61	adamant-1-ylmethyl	3-(2-(morpholin-4-yl)ethoxy)carbonyl	H	+	iii
62	adamant-1-ylmethyl	3-amino	H	+	iii
63	adamant-1-ylmethyl	(1,2-dihydroxypropyl)amino	H	+	iii
64	adamant-1-ylmethyl	(1,2-dihydroxypropyl)amino	H	rac	iii
65	adamant-1-ylmethyl	3-acetamido	H	rac	iii
66	adamant-1-ylmethyl	3-formylamino	H	rac	iii
67	adamant-1-ylethyl	3-*N*,*N*-dimethylamino	H	rac	v
68	adamant-1-ylethyl	3-methylthiophenyl	H	rac	v
69	adamant-2-yl	3-*N*,*N*-dimethylamino	H	rac	v
70	adamant-2-yl	3-(tetrazol-5-yl)	H	rac	ii
71	bicyclo[2.2.1]-2-heptyl	3-*N*,*N*-dimethylamino	H	rac	iii
72	bicyclo[2.2.1]-2-heptyl	3-chloro	H	rac	iii
73	adamant-2-ylmethyl	3-*N*,*N*-dimethylamino	H	rac	iii

is the calculated molar refractivity;[34] Sb is Austel's parameter;[35] and D_1 is a dummy variable that accounts for the presence ($D = 1$) or absence ($D = 0$) of branching on the first carbon atom of the substituent. The analysis of the PLS model reveals that the lipophilicity and the steric hindrance of the substituent are critical parameters in view of optimizing the affinity for the CCK-B receptor subtype with respect to the substitution at position N-1.

On the basis of the previous analysis, and with the aim of defining a better compromise for both the affinity and the selectivity with respect to the substituent at

Table 2. pK_i Values[a] for 1-Alkyl-5-aryl-3-ureido-1,5-benzodiazepine-2,4-diones in CCK-B and CCK-A Binding Assays



compd	R_1	R_2	R_3	stereo	CCK-A pK_i[b]	CCK-B pK_i[b]	B/A[c]
11	butyl	H	H	rac	6.26	8.21	89
12	3-methylbut-1-yl	H	H	rac	6.49	8.81	209
13	3-methylbut-1-yl	H	H	+	5.34	8.00	457
14	3-methylbut-1-yl	H	H	−	6.74	8.38	44
15	3-methylbut-1-yl	H	F	rac	6.71	8.11	25
16	1,3-dimethylbut-1-yl	H	H	rac	6.94	8.68	55
17	2,3-dimethylbut-1-yl	H	H	rac	6.91	8.95	110
18	3,3-dimethylbut-1-yl	H	H	rac	6.95	9.17	166
19	3,3-dimethylbut-1-yl	H	F	rac	7.15	9.02	74
20	1-cyclopentyl-prop-2-yl	H	H	rac	7.11	8.45	22
21	2-cyclopentylethyl	H	F	rac	7.00	9.14	138
22	2-phenylethyl	H	H	rac	6.57	8.08	32
23	adamant-1-ylmethyl	H	H	rac	6.15	8.64	309
24 (GV150013)	adamant-1-ylmethy	H	H	+	5.79	9.03	1738
25	adamant-1-ylmethy	H	H	−	6.32	7.08	6
26	2-(adamant-1-yl)ethyl	H	H	rac	6.66	7.47	6
27	adamant-2-yl	H	H	rac	6.66	7.94	19
28	bicyclo[2.2.1]-hept-2-yl	H	H	rac	6.60	8.81	162
29	adamant-2-ylmethyl	H	H	rac	7.08	8.71	48
30	3-methylbut-1-yl	3-*N*,*N*-dimethylamino	F	rac	6.90	9.60	501
31	3-methylbut-1-yl	3-*N*,*N*-dimethylamino	F	+	6.70	9.68	933
32	3-methylbut-1-yl	3-*N*,*N*-dimethylamino	F	−	7.14	8.73	39
33	3-methylbut-1-yl	3-methylthio	F	rac	7.44	9.48	110
34	3,3-dimethylbut-1-yl	3-*N*,*N*-dimethylamino	H	rac	7.65	9.52	74
35	3,3-dimethylbut-1-yl	3-methylthio	H	rac	8.13	9.31	15
36	3,3-dimethylbut-1-yl	3-cyano	H	rac	7.01	9.19	151
37	3,3-dimethylbut-1-yl	3-(tetrazol-5-yl)	H	rac	7.64	9.54	70
38	3,3-dimethylbut-1-yl	3-[2-(2,2-dimethylethyl)tetrazol-5-yl]	H	rac	7.31	8.61	20
39	3,3-dimethylbut-1-yl	3-trifluoromethoxy	H	rac	6.95	8.54	38
40	3,3-dimethylbut-1-yl	3-methylthio	F	rac	7.93	9.14	16
41	3,3-dimethylbut-1-yl	3-*N*,*N*-dimethylamino	F	rac	7.71	9.22	32
42	2-cyclopentylprop-2-yl	3-(tetrazol-5-yl)	H	rac	7.33	8.82	31
43	2-cyclopentylethyl	3-*N*,*N*-dimethylamino	F	rac	7.32	9.17	71
44	2-cyclopentylethyl	4-*N*,*N*-dimethylamino	F	rac	6.18	8.33	141
45	2-cyclopentylethyl	3-methylthio	F	rac	7.65	9.12	30
46	2-cyclopentylethyl	3-(tetrazol-5-yl)	F	rac	6.92	9.65	468
47	adamant-1-ylmethyl	3-hydroxy	H	+	5.80	9.24	550
48	adamant-1-ylmethyl	3-methyl	H	rac	6.60	8.81	162
49	adamant-1-ylmethyl	3-nitro	H	rac	6.52	8.72	158
50	adamant-1-ylmethyl	3-bromo	H	rac	6.72	8.42	48
51	adamant-1-ylmethyl	3-ethoxycarbonyl	H	rac	6.09	8.53	275
52	adamant-1-ylmethyl	3-carboxy	H	rac	6.20	9.01	646
53	adamant-1-ylmethyl	3-*N*,*N*-dimethylamino	H	rac	6.35	8.95	398
54	adamant-1-ylmethyl	3-hydroxymethyl	H	+	5.67	9.75	12023
55	adamant-1-ylmethyl	3-(morpholin-4-yl)methyl	H	+	4.70	8.52	6607
56	adamant-1-ylmethyl	4-bromo	H	+	5.46	8.85	2455
57	adamant-1-ylmethyl	3-bromo	H	+	5.81	9.08	613
58	adamant-1-ylmethyl	4-(3-ethoxycarbonylpropyl)oxy	H	+	<5	8.28	>1905
59	adamant-1-ylmethyl	4-(3-carboxypropyl)oxy	H	+	<5	8.42	>2630
60	adamant-1-ylmethyl	4-hydroxy	H	+	4.69	9.18	30903
61	adamant-1-ylmethyl	3-(2-(morpholin-4-yl)ethoxy)carbonyl	H	+	6.47	9.25	603
62	adamant-1-ylmethyl	3-amino	H	+	5.39	9.53	13804
63	adamant-1-ylmethyl	(1,2-dihydroxy propyl)amino	H	+	5.13	9.17	10965
64	adamant-1-ylmethyl	(1,2-dihydroxypropyl)amino	H	rac	6.20	8.90	575
65	adamant-1-ylmethyl	3-acetamido	H	rac	5.82	8.88	591
66	adamant-1-ylmethyl	3-formyl	H	rac	5.95	9.02	1175
67	adamant-1ylethyl	3-*N*,*N*-dimethylamino	H	rac	6.53	7.88	22
68	adamant-1ylethyl	3-methylthio	H	rac	6.60	7.22	4
69	adamant-2-yl	3-*N*,*N*-dimethylamino	H	rac	6.85	8.63	60
70	adamant-2-yl	3-(tetrazol-5-yl)	H	rac	7.01	8.68	47
71	bicyclo[2.2.1]-2-heptyl	3-*N*,*N*-dimethylamino	H	rac	7.35	8.99	40
72	bicyclo[2.2.1]-2-heptyl	3-chloro	H	rac	7.32	8.76	28
73	adamant-2-ylmethyl	3-*N*,*N*-dimethylamino	H	rac	7.2	8.9	54

[a] Inhibition of binding of [^{3}H]pCCK-8. [b] Mean value of three experiments. [c] Selectivity factor between CCK-B and CCK-A receptors.

position N-1, a series of compounds bearing different groups at position N-1, while retaining or not retaining the substituents at other positions, were synthesized. Relevant results are reported in Table 2. The introduction of bulky cyclo-bridged groups such as adamantyl is well-accepted in terms of receptor affinity, while important changes in the selectivity were obtained by varying either the length of the chain linking such a group to the 1,5-benzodiazepinic nucleus or the position by which the cyclo-bridged group is linked to the chain.

Table 3. pK_i Values[a] for GV150013 and Reference Compounds in CCK-B and CCK-A Assays

compd	hCCK-B pK_i ± SEM	*n*	guinea-pig CCK-B pK_i ± SEM	*n*	rat CCK-B pK_i ± SEM	*n*	rat CCK-A pK_i ± SEM	*n*
GV150013 (**24**)	9.43 ± 0.12	4	9.15 ± 0.04	14	8.55 ± 0.05	4	5.83 ± 0.05	11
L-365,260	8.80 ± 0.06	4	8.53 ± 0.11	4	7.91 ± 0.05	4	6.48 ± 0.09	3
PD134,308	9.45 ± 0.06	3	8.73 ± 0.06	10	8.03 ± 0.04	3	6.16 ± 0.06	6
L-364,718	7.53 ± 0.10	3	7.06 ± 0.02	3	6.57 ± 0.10	4	9.83 ± 0.05	4

[a] Values in displacing [^{3}H]CCK-8S from rat pancreatic, guinea-pig, and rat membranes and comparison with human CCK-B receptor affinities; data are means of *n* experiments. Experiments were performed on a membrane preparation obtained from a transfected HeLa cell line.

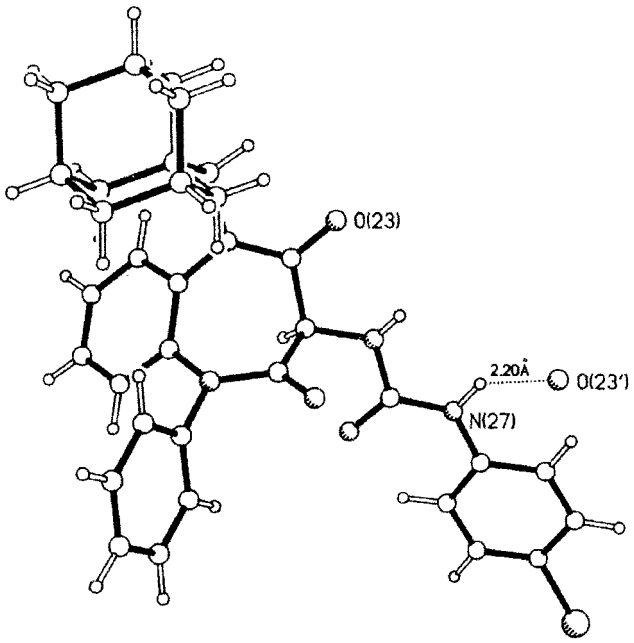


Figure 3. Structure and conformation of **56** as determined by X-ray crystallography.

Thus, for example, the 1-adamantyl derivatives were more CCK-B-selective than the corresponding 2-adamantyl ones. Although a SAR cannot be established yet for the whole substitution pattern, some preliminary comments can be made other than those reported for the substitution in position N-1: (1) a meta substituent on the ureidic phenyl (e.g. dimethylamino or methylthio) may enhance CCK-B receptor affinity (this is however dependent on the substituent at N-1 position); (2) introduction of an *o*-fluoro substituent at N-5 phenyl proved to be beneficial particularly in combination with a *m*-dimethylamino substituent at the urea side chain and a branched alkyl at N-1; (3) substitution with halogens at the fused aromatic ring was not as efficient as in other series (e.g. carbamates).[16,30,31]

Finally, the separation of the isomers of the most interesting compounds revealed that for the current series the (+)-isomers are more CCK-B-selective than the corresponding (−)-ones, as a result of either retention or slight increase in CCK-B receptor affinity associated with a drop of CCK-A potency. This effect was observed for the N-5 aryl derivatives, and it is particularly relevant in the case of the 1-adamantylmethyl series. As a result of this evaluation, GV150013 (Figure 4) has emerged as a potent and selective CCK-B antagonist and has progressed into development. Furthermore, the X-ray structure of GV182635, **56**, was aligned to a possible pharmacophore model of eight potent and selective peptoidic derivatives synthesized at Parke Davis Lab.[10] The pharmacophore model, developed in house, was identified with the use of the

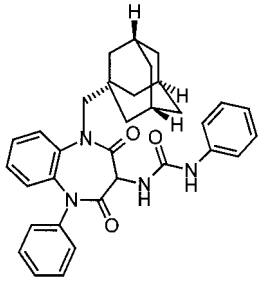


Figure 4. Chemical structure of GV150013

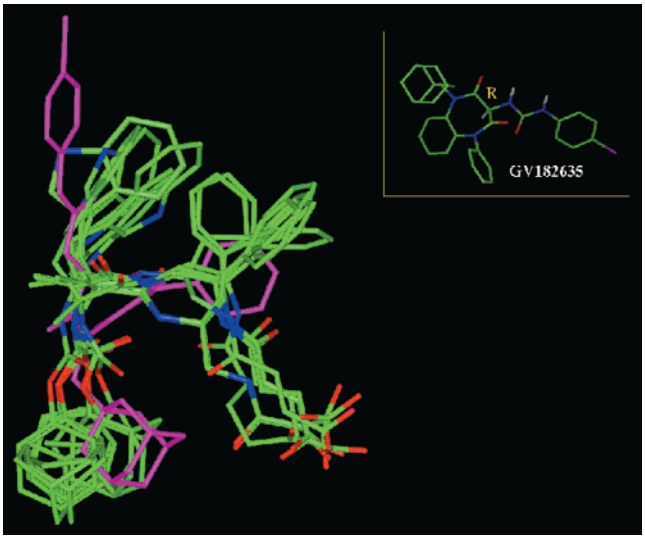


Figure 5. Superimposition of GV182635 (purple) with the pharmacophore model.

active analogue approach (AAA)[37] mode, implemented within Sybyl,[38] followed by molecular dynamics simulations (MD) within Discover[39] (CVFF force field)[40] with distance restraints taken from the pharmacophore AAA distance maps.[36] The superimposition was carried out by aligning the adamantyl group, the ureidic substituent, and the phenyl ring of the benzodiazepine derivative on the corresponding pharmacophore features (the adamantyl group, the indole, and the phenyl ring) of the peptoidic derivatives, respectively. As can be seen in Figure 5, the 1,5-BDZ structure, as exemplified by **56**, exhibits a good alignment to the pharmacophore model, and the seven-membered ring could mimick the γ-turn at the Trp residue of the peptoidic derivatives.

In Table 3, the binding profile of GV150013 is reported and compared with values obtained for two other CCK-B antagonists, PD134,308 and L365,260. GV150013 shows higher affinity than the reference compounds in all the three species in wich the binding for the CCK-B receptor subtypes was assayed, except in the human recombinant assay, where it demonstrated the same affinity as PD134,308. Furthermore, GV150013 shows the higher B/A selectivity in all the

Table 4. GV150013 in Animal Model of Anxiety

model	ED_{50} ($\mu g \cdot kg^{-1}$)	route
mouse black/white box	0.05	po
mouse black/white box	0.03	iv
rat social interaction[a]	1.6	po
marmoset human threat	0.02	sc
rat vogel	no effect up to $\mu g \cdot kg^{-1}$	

[a] Against FG 7142, 10 $mg \cdot kg^{-1}$, ip.

species. Interestingly, both GV150013 and the reference CCK-B antagonists compounds exhibited their highest affinity against the human receptor and their lowest in the rat assay. The data obtained from radioligand binding assays has been confirmed in functional assays for CCK-B and CCK-A receptors. In the guinea-pig myenteric plexus where both receptor subtypes are found, a pK_B of 8.9 ± 0.3 was determined for GV150013 against selective CCK-B agonists and 5.9 ± 0.2 against a selective CCK-A agonist.[41] In the guinea-pig gallbladder, a CCK-A-selective tissue, GV150013 had a pK_B of 5.8 ± 0.1. In the isolated rat gastric mucosa, an assay for gastrin receptors, GV150013 was less potent as an antagonist than in the neuronal assays and a pK_B of 7.4 ± 0.2 was determined against pentagastrin-induced acid secretion. This indicates that GV150013 may discriminate between the classical CCK-B receptor and the stomach gastrin receptor.

Finally, GV150013 has shown activity in a number of animal models of anxiety as can been seen from the ED_{50} values given in Table 4. In the mouse black/white box test GV150013 increased the time that naive mice remained in a brightly illuminated section of an activity box. The effect was dose-related, and significant increases were measured at 0.1, 0.3, and 1.0 μg/kg. Similar anxiolytic effects were seen in the rat social interaction test and the marmoset human threat test.[29] In all of the anxiolytic models used, GV150013 displayed similar efficacy to PD134,308 and to a standard benzodiazepine (diazepam in the mouse studies and chlordiazepoxide in the rat and marmoset). GV150013 did not show tolerance or rebound anxiogenesis upon withdrawal after chronic treatment (7 days at 0.3 μg/kg, po) in the mouse black/white box, while diazepam (2.5 mg/kg, po) carried through in parallel exhibited a marked reduction of effect and a significant rebound upon cessation of dosing. In general pharmacological studies, GV150013 showed no effect up to 3 mg/kg, po in the rota-rod test (motor function), in passive avoidance (learning and memory), and on pentobarbitone sleeping time (interaction with metabolic enzymes). No gross behavior effects were seen with the compound up to a dose of 10 mg/kg, po.

Conclusion

A novel class of 1,5-benzodiazepines was explored with the aim of identifying a new potent and selective CCK-B antagonist. The molecular structure of compounds belonging to this class can be efficiently manipulated to get potent and selective CCK-B antagonists. The substitution of the N-1 position with a suitable side chain gave potent antagonists endowed with nanomolar affinity at the CCK-B binding site. Among them, GV150013 exhibits high affinity for the CCK-B receptor, high selectivity against CCK-A receptors, and anxiolytic activity in a number of animal models with an activity in the range 0.3−3 μg/kg, depending on the species. Moreover, GV150013 is devoid of any significant side effects and is a compound that might be useful in the treatment of anxiety, panic, and sleep disorders.

Experimental Section

In the preparations and examples, unless otherwise stated: Melting points (mp) were determined on a Büchi melting point apparatus and are uncorrected. All temperatures refer to °C. Infrared spectra were measured on a Bruker IFS 48 (FT) spectrometer in chloroform-d_1 solutions or in Nujol mull. Proton magnetic resonance (^{1}H NMR) spectra were recorded at room temperature either on a Varian Unity 400 operating at 400 MHz or on a Varian VXRS 5000 operating at 300 MHz. All spectra are in $CDCl_3$ solution (unless otherwise specified) and referenced to residual solvent signal. Chemical shifts are reported in ppm downfield from Me_4Si and are assigned as singlets (s), doublets (d), doublet of doublets (dd) or multiplets (m). Column chromatography was carried out over silica gel 60 (Merck AG Darmstadt, Germany). Mass spectra were recorded on a VG-4 triple quadrupole Fison instrument in FAB mode. Elemental analyses were performed by our analytical group on Carlo Erba elemental analyzer. Optical rotations were determined at 20 °C with a Jasco DIP 360 Instrument (l = 10 cm, cell volume = 1 mL, λ = 589 nm). Solutions were dried over anhydrous sodium sulfate. Methylene chloride was redistilled over calcium hydride; tetrahydrofuran was redistilled over sodium; ethyl ether was redistilled over sodium; ethyl acetate was dried over activated molecular sieves. The following abbreviations are used in the text: EA = ethyl acetate, CH = cyclohexane, P = petroleum ether 40−60 °C, THF = tetrahydrofuran, MC = methylene chloride, EE = ethyl ether, petrol = petroleum ether, bp 40−60 °C. TLC refers to thin-layer chromatography on silica plates using Merck silica gel 60 F-254 glass plates (0.25 mm). All the compounds are intended as racemic mixtures unless otherwise indicated.

General Procedure for Alkylation of Intermediate 2 To Obtain Compounds of General Formula 3: Route A (Scheme 1). 1-*N*-(Adamant-1-ylmethyl)-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (3m). Sodium hydride 80% dispersion in oil (1.18 g, 30 mmol) was added to a solution of 2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine **(2)**[17] (7.0 g, 20 mmol) in dry DMF (400 mL). The mixture was heated to 130 °C for 45 min under a nitrogen atmosphere. Next, a solution of 1-adamantanemethanol−methanesulfonate (7.58 g, 20 mmol) in dry DMF (70 mL) was added dropwise. The mixture was stirred at 150 °C for 6 h, then continued at 23 °C for 48 h. The reaction mixture was then diluted with ethyl acetate (400 mL), washed with brine (4 × 400 mL) dried and concentrated in vacuo to an oil wich was purified by flash chromatography (eluting in gradient from CH−EA 80:20 to EA) to give 1.97 g of final compound **3m** as a white solid (18%): mp 180−2 °C; TLC R_f = 0.42 (EA/CH, 1:1); MS (FAB) *m/e* 402 (MH^+); IR ν_{max}1695 and 1670 (C=O, C=C) cm^{-1}; ^{1}H NMR δ 7.50−7.10 (m, 8H); 6.95 (d, 1H); 4.53 (d, 1H); 3.32 (d), 3.50 (s, 2H); 1.89 (m, 3H); 1.70−1.40 (m, 12H).

Analytical data for representative compounds are as follows.

1-*N*-Butyl-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (3a): TLC R_f = 0.53 (EA/CH, 3:7); ^{1}H NMR δ 7.50−7.10 (m, 8H); 6.99 (d, 1H); 4.50 (m, 1H); 3.65 (m, 1H); 3.50 (s, 2H); 1.60 (m, 2H); 1.40 (m, 2H); 0.90 (t, 3H).

2,4-Dioxo-1-*N*-(3-methylbut-1-yl)-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (3b): TLC R_f = 0.36 (EA/CH, 1:1); IR ν_{max} 1695 and 1668 (C=O) and (C=C) cm^{-1}; ^{1}H NMR δ 7.44−7.10 (m); 6.94 (d); 6.94 (d, 1H); 4.55 (m,); 3.63 (m); 3.47(s); 1.52 (m); 1.48 (m); 0.92 (d); 0.89 (d).

1-*N*-(2,3-Dimethylbut-1-yl)-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (3e): TLC R_f = 0.40 (EA/CH, 1:1); IR ν_{max}1695, 1668 (C=O) and (C=C) cm^{-1}; ^{1}H NMR δ 7.46−7.36 (m, 3H); 7.35−7.2 (m, 3H);7.19−7.08 (m, 1H); 6.94 (dd, 1H); 4.65 and 4.52 (2dd, 1H); 3.58 and 3.38 (dd,

1H); 3.51 and 3.49 (2s, 1H); 1.8−1.6 (m, 2H); 0.91−0.82 (3d, 6H); 0.79 and 0.78 (2d, 3H).

1-*N*-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (3f): TLC R_f = 0.39 (EA/CH, 1:1); MS (FAB) *m/e* 337 (MH^+); IR ν_{max}1713 (C═O) cm^{-1}; ^1H NMR δ 7.48−7.08 (m, 8H); 6.95 (dd, 1H); 4.60−4.40 (m, 1H); 3.7−3.55 (m, 1H); 3.49 (s, 2H); 1.52−1.40 (m, 2H); 0.95 (s, 9H).

2,4-Dioxo-5-*N*-phenyl-1-*N*-(2-phenylethyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (3l): TLC R_f = 0.27 (EA/CH, 1:1); IR ν_{max}1695 and 1668 (C═O), 1599 (C═C) cm^{-1}; ^1H NMR δ 7.45−6.90 (m, 14H); 4.75 (m, 1H); 4.0−3.80 (m, 1H); 3.516 (s, 2H); 2.964 (t, 2H).

1-[2-(1-Adamantyl)ethyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (3n): TLC R_f = 0.42 (EA/CH, 1:1); MS (FAB) *m/e* 415 (MH^+); IR ν_{max} 1695 and 1668 (C═O) cm^{-1}; ^1H NMR δ 7.42−7.36 (m, 3H); 7.30 (m, 1H); 7.26 (d, 1H); 7.19 (m, 2H); 7.11 (m, 1H); 6.93 (dd, 1H); 4.50 (m, 1H); 3.64 (m, 1H); 3.46 (s, 2H); 1.94 (bs, 3H); 1.74 (m, 6H); 1.5 (m, 6H); 1.37 (m, 2H).

General Procedure To Obtain Compounds of General Formula 4: Route A (Scheme 1). 1-*N*-(Adamant-1-ylmethyl)-3-azido-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (4m). A solution of the intermediate **3** (1.69 g 4.29 mmol) in dry THF (40 mL) was added to potassium *tert*-butoxide (0.7 g, 6.23 mmol) in dry THF (30 mL) cooled to −78 °C under a nitrogen atmosphere. The reaction mixture was stirred at −78 °C for 30 min, then a cooled solution (−78 °C) of 2,4,6-triisopropylbenzenesulfonyl azide (1.50 g, 5.08 mmol) in dry THF (30 mL) was added. After 5 min glacial acetic acid (0.24 mL) was added and the solution was allowed to warm to 23 °C and stirred for 24 h. The reaction mixture was diluted with EA (200 mL) and washed with brine, saturated sodium hydrogen carbonate solution, water, 10% hydrochloric acid solution and brine (2 × 100 mL). The combined organic extracts were dried and concentrated in vacuo to give after flash chromatography on silica and EA/CH, 3:7 as eluants, the final compound **4m** as a white solid (0.98 g, 0.56 mmol, 52%): TLC R_f = 0.73 (EA/CH, 1:1); IR ν_{max} 2112 (N_3), 1690, 1666 (C═O) and (C═C) cm^{-1}; ^1H NMR δ 7.5−7.10 (m, 9H); 6.99(d, 1H); 4.53 (m, 1H); 4.20 (s, 1H); 3.39 (d, 1H); 1.90 (m, 3H); 1.7−1.35 (m, 12).

Analytical data for representative compounds are as follows.

3-Azido-1-*N*-butyl-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (4a): TLC R_f = 0.67 (EA/CH, 4:6); IR ν_{max} 2114 (N_3), 1691−1666 (C═O) cm^{-1}; ^1H NMR δ 7.50−7.00 (m, 8H); 6.90 (d, 1H); 4.60 (m, 1H); 3.70 (m, 1H); 1.8−1.0 (m, 4H); 0.80 (t, 3H).

3-Azido-2,4-dioxo-1-*N*-(3-methylbut-1-yl)-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (4b): TLC R_f = 0.30 (EA/CH, 4:6); MS (FAB) *m/e* 364 (MH^+); IR ν_{max} 2122 (N_3), 1709 (C═O) cm^{-1}; ^1H NMR δ 7.45−7.00 (m, 8H); 6.98 (d, 1H); 4.54 (m, 1H); 4.20 (s, 1H); 3.70 (m, 1H); 1.62−1.45 (m, 3H); 0.93 (d, 3H); 0.91 (m, 3H).

3-Azido-1-*N*-(2,3-dimethylbut-1-yl)-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (4e): TLC R_f = 0.73 (EA/CH, 1:1); IR ν_{max} 2114 (N_3), 1691, 1666 (C═O) cm^{-1}; ^1H NMR δ 7.46 7.14 (m, 8H); 6.98 (2d, 1H); 4.65 and 4.53 (2dd, 1H); 4.21 and 4.19 (2s, 1H); 3.64 and 3.44 (2dd, 1H); 1.82−1.70 (m, 1H); 1.64−1.48 (m, 1H); 0.91 and 0.78 (2d, 3H); 0.84 and 0.83 (2d, 6H).

3-Azido-1-*N*-(3,3-dimethylbut-1-yl)-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (4f): TLC R_f = 0.73 (EA/CH, 1:1); MS (FAB) *m/e* 378 (MH^+); IR ν_{max} 2127 (N_3), 1693, 1666 (C═O), 1597 (C═C) cm^{-1}; ^1H NMR δ 7.44−7.40 (m, 3H); 7.38−7.31 (m, 2H); 7.24−7.17 (m, 3H); 6.999 (dd, 1H); 4.537−4.434 (m, 1H); 4.20 (s, 1H); 3.775−3.674 (m, 1H); 1.523 (m, 2H); 0.967 (s, 9H).

3-Azido-2,4-dioxo-5-*N*-phenyl-1-*N*-(2-phenylethyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (4l): TLC R_f = 0.57 (EA/CH, 1:1); MS (FAB) *m/e* 398 (MH^+); IR ν_{max} 2122 (N_3), 1709, 1684 (C═O) cm^{-1}; ^1H NMR δ 7.50−6.95 (m, 14H); 4.234 (s, 1H); 4.80−4.60 (m, 1H); 4.0−3.8 (m, 1H); 2.98 (m, 2H).

1-*N*-(2-Adamant-1-ylethyl)-3-azido-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (4n): TLC R_f = 0.68 (EA/CH, 1:1); MS (FAB) *m/e* 456 (MH^+); IR ν_{max} 2122 (N_3), 1709, 1678 (C═O), 1601 (C═C) cm^{-1}; ^1H NMR δ 7.50−7.15 (m, 8H); 6.99 (dd, 1H); 4.49 (m, 1H); 4.19 (s, 1H); 3.72 (m, 1H); 1.97 (bs, 3H); 1.9−1.3 (m, 14H).

General Procedure To Obtain Compounds of General Formula 5 via Reduction of Azido Intermediate 4: Route A (Scheme 1). 1-*N*-(Adamant-1-ylmethyl)-3-amino-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5m). 5% $Pd/CaCO_3$ (0.51 g) was added to a solution of the intermediate **4m** (0.92 g, 2.08 mmol) in EA (50 mL) and ethanol (50 mL) and the mixture was hydrogenated at 1 atm for 5 h. The catalyst was filtered off and the solvent evaporated in vacuo to small volume. The residue was diluted with dichloromethane (50 mL), washed with brine (3 × 25 mL), dried and concentrated in vacuo. Purification by flash chromatography (eluting with EA−MeOH 95:5) gave the title compound **5m** as a white foam (0.75 g, 1.8 mmol. 87%): TLC R_f = 0.51 (MC/MeOH, 9:1); MS (FAB) *m/e* 416 (MH^+); IR ν_{max} 3369 (NH_2), 1701−1672 (C═O) cm^{-1}; ^1H NMR δ 7.47 (dd, 1H); 7.40−7.30 (m, 5H); 7.23 (td, 1H); 7.15 (td, 1H); 6.94 (dd, 1H); 4.52 (d, 1H); 3.38 (d, 1H); 4.22 (s, 1H); 2.30−1.70 (m, 2H); 1.82 (m, 3H); 1.70−1.30 (m, 12H).

Analytical data for representative compounds are as follows.

3-Amino-1-*N*-butyl-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5a): TLC R_f = 0.25 (MC/MeOH, 95:5); IR ν_{max}3710 (NH_2), 1701, 1668 (C═O) cm^{-1}; ^1H NMR δ 7.50−7.15 (m, 8H); 6.99 (d, 1H); 4.50 (m, 1H); 4.25 (s, 1H); 3.70 (m, 1H); 1.80−1.2 (m, 6H); 0.90 (t, 3H).

3-Amino-2,4-dioxo-1-*N*-(3-methylbut-1-yl)-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5b): TLC R_f = 0.55 (MC/MeOH, 95:5); MS (FAB) *m/e* 339 (MH^+); IR ν_{max} 3393 (NH); 1705−1670 (C═O), 1595 (C═C) cm^{-1}; ^1H NMR δ 7.45−7.1(m, 8H); 6.95 (d, 1H); 4.54 (m, 1H); 3.67 (m, 1H); 4.22 (s, 1H); 1.92 (bs, 2H); 1.55 (m, 1H); 1.47 (m, 2H); 0.91(d, 3H); 0.88 (d, 3H).

3-Amino-1-*N*-(2,3-dimethylbutyl)-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5e): TLC R_f = 0.55 (EA/MeOH, 9:1); IR ν_{max} 3371 (NH_2); 1701, 1668 (C═O), 1593 (C═C) cm^{-1}; ^1H NMR δ 7.46−7.12 (m, 8H); 6.94 (dd, 1H); 4.66 and 4.53 (2 dd, 1H); 4.24 and 4.22 (2 s, 1H); 3.64 and 3.44 (2 dd, 1H); 1.8−1.6 (m, 1H); 1.6−1.4 (m, 1H); 2.0−1.4 (bs, 2H); 0.9 and 0.84 (2d, 3H); 0.75 and 0.77 (2d, 3H); 0.81 and 0.84 (2 d, 3H).

3-Amino-1-*N*-(3,3-dimethylbutyl)-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5f): TLC R_f = 0.46 (MC/MeOH, 9:1); IR ν_{max} 1701, 1670 (C═O), 1593 (C═C) cm^{-1}; ^1H NMR δ 7.47−7.12 (m, 8H); 6.91 (dd, 1H); 4.58−4.40 (m, 1H); 3.80−3.63 (m, 1H); 4.24 (s, 1H); 1.54−1.45 (m, 2H); 1.85−1.55 (m, 2H); 0.96 (s, 9H).

3-Amino-2,4-dioxo-5-*N*-phenyl-1-*N*-(2-phenylethyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5l): TLC R_f = 0.1 (MC/MeOH, 9:1); MS (FAB) *m/e* 372 (MH^+); IR ν_{max}1707 (C═O), 1595 (C═C) cm^{-1}; ^1H NMR δ 7.50−7.15 (m, 13H); 7.03 (md, 2H); 6.95 (dd, 1H); 4.72 (m, 1H); 4.26 (s, 1H); 3.93 (m, 1H); 2.95 (t, 2H).

1-*N*-(2-Adamant-1-ylethyl)-3-amino-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5n): TLC R_f = 0.62 (MC/MeOH, 9:1); MS (FAB) *m/e* 430 (MH^+); IR ν_{max} 3447−2671 (NH_2), 1707,1686 (C═O) cm^{-1}; ^1H NMR δ 7.48−7.24 (m, 4H); 7.24−7.12 (m, 4H); 6.95 (dd, 1H); 4.56−4.4 (m, 1H); 4.23 (s, 1H); 3.78−3.64 (m, 1H); 2.0−1.3 (m, 19H).

General Procedure for Alkylation of Amines 1 and 6 To Obtain Compounds of General Formula 7: Route B, Method A (Scheme 2). 2-Fluoro-2′-(3-methylbut-1-yl)-aminodiphenylamine (7c). Bromo-3-methylbutane (4.33 mL, 35 mmol) was added to a solution of 2-amino-2′-fluorodiphenylamine[42] **(6)** (7.0 g, 35 mmol) and sodium iodide (5.24 g, 35 mmol) in dimethylformamide (250 mL) under a nitrogen atmosphere. The solution was stirred at 120 °C for 8 h, then cooled to room temperature, diluted with water (300 mL) and extracted with diethyl ether (2 × 250 mL). The combined organic extracts were washed with brine (300 mL), dried and

concentrated in vacuo to an oil, which was purified by flash chromatography (eluting with CH−EA 95:5) to give 6.3 g of title compound **7c** as a yellow oil (66%): TLC $R_f = 0.75$ (CH/EA, 9:1); MS (FAB) *m/e* 273 (MH^+); IR ν_{max} 3410 (NH) and 1620 (C=C) cm^{-1}; ^1H NMR δ 7.14−6.6 (m, 8H); 5.25 (bs, 1H); 4.09 (bs, 1H); 3.14 (t, 2H); 1.65 (m, 1H) 1.49 (m 2H); 0.91 (d, 6H).

General Procedure for Alkylation of Amines 1 and 6 To Obtain Compounds of General Formula 7: Route B, Method B_1 (Scheme 2). 2-(3,3-Dimethylbut-1-yl)amino-2′-fluorodiphenylamine (7g). Sodium borohydride (22.7 g, 600 mmol) was added portionwise to a mixture of 2-amino-2′-fluorodiphenylamine[42] **(6)** (8.0 g, 40 mmol), sodium acetate trihydrate (16.33 g, 120 mmol) and 3,3-dimethylbutyraldehyde (5 mL, 40 mmol) in acetic acid (12.8 mL), water (50 mL) and ethanol (40 mL) cooled to 0 °C. The solution was stirred at 23 °C for 30 min, then diluted with ethyl acetate (300 mL). The organic layer was washed with a 10% solution of sodium hydroxide (3 × 200 mL) and brine (200 mL), dried and concentrated in vacuo to an oil, which was purified by flash chromatography (eluting with CH−EA 9:1) to give 7.44 g of compound **7g** as a yellow oil (65%): TLC $R_f = 0.85$ (CH/EA, 9:1); IR ν_{max} 3408 (NH), 1618 and 1603 (C=C) cm^{-1}; ^1H NMR δ 7.2−7.0 (m, 3H); 6.93 (dt, 1H); 6.8−6.6 (m, 4H); 6.26 (d, 1H); 4.07 (t, 1H); 3.15 (m, 2H); 1.6−1.5 (m, 2H); 0.96 (s, 9H).

Analytcal data for representative compounds are as follows.

2-(1,3-Dimethylbut-1-yl)aminodiphenylamine(7d). Starting from commercially available 2-aminodiphenylamine **(1)**: TLC $R_f = 0.79$ (CH/EA, 9:1); MS (FAB) *m/e* 268 (MH^+); IR ν_{max} 3420 (NH), 1599, 1514 and 1497 (C=C) cm^{-1}; ^1H NMR δ 7.3−7.05 (m, 3H); 6.85−6.6 (m, 6H); 5.01 (bs, 1H); 3.97 (b, 1H), 3.56 (m, 1H); 1.68 (m, 1H); 1.51−1.37 (m, 1H), 1.14 (d, 3H); 1.3−1.15 (m, 1H); 0.91 (d, 3H); 0.88 (d, 3H).

2-(3-Cyclopentylpropen-2-yl)aminodiphenylamine (7h). Starting from commercially available 2-aminodiphenylamine **(1):** TLC $R_f = 0.58$ (CH/EA 3:1); IR ν_{max} 3373 (NH), 1599 (C=C) cm^{-1}; ^1H NMR δ 7.19−7.14 (m, 2H); 7.11−7.06 (m, 2H); 6.78 (t, 1H); 6.71−6.6 (m, 4H); 4.99 (bs, 1H); 3.97 (bs, 1H); 3.49 (m, 1H); 1.88 (m, 1H); 1.70 (m, 1H); 1.58 (m, 1H); 1.64−1.00 (m, 6H); 1.13 (d, 3H).

2-(2-Cyclopentylethyl)amino-2′-fluorodiphenylamine (7i). Starting from 2-amino-2′-fluorodiphenylamine[42] **(6):** TLC $R_f = 0.78$ (CH/EA 9:1); IR ν_{max} 3398 (NH); 1618−1605 (C=C) cm^{-1}; ^1H NMR δ 7.18−7.07 (m, 2H); 7.03 (m, 1H); 6.9 (m, 1H); 6.72 (m, 1H); 6.76−6.58 (m, 3H); 5.25 (bs, 1H); 4.12 (bs, 1H); 3.13 (t, 2H); 1.90−1.05 (m, 11H).

2-(Adamant-2-yl)aminodiphenylamine (7o). Starting from commercially available 2-aminodiphenylamine **(1):** TLC $R_f = 0.73$ (CH/EA 9:1); IR ν_{max} 3400 (NH); 1605 (C=C) cm^{-1}; ^1H NMR δ 7.18 (m, 2H); 7.07 (m, 2H); 6.79 (t, 1H); 6.72 (m, 2H); 6.67−6.6 (m. 2H); 5.05 (bs, 1H); 4.51 (bs, 1H); 3.53 (bs, 1H); 2.00−1.4 (m, 14H).

2-(Adamant-1-ylmethyl)aminodiphenylamine (7m). Starting from commercially available 2-aminodiphenylamine **(1) (**55%): TLC $R_f = 0.59$ (CH/EA 8:2); MS (FAB) *m/e* 332 (MH^+); IR ν_{max} 3427, 3379 (NH); 1599 (C=C) cm^{-1}; ^1H NMR δ 7.18 (m, 2H); 7.07 (m, 2H); 6.80 (dt, 1H); 6.72 (d+m, 3H) 6.62 (dt, 1H); 5.07 (bs, 1H); 4.19 (bs, 1H); 2.78 (d, 2H); 1.92 (m, 3H); 1.74−1.40 (m, 12H).

2-(Adamant-2-ylmethyl)aminodiphenylamine (7q). From 2-adamantanecarboxaldehyde[43] and 2-aminodiphenylamine **(1)**: TLC $R_f = 0.86$ (CH/EA 8:2); MS (FAB) *m/e* 332 (MH^+); IR ν_{max} 3436 (NH); 1599 (C=C) cm^{-1}; ^1H NMR δ 7.25−7.07 (m, 4H); 6.85−6.6 (m, 5H); 6.67−6.6 (m); 5.027 (s, 1H); 4.10 (s, 1H); 3.22 (d, 2H); 1.95−1.5 (m, 15H).

General Procedure for Alkylation of Amines 1 and 6 To Obtain Compounds of General Formula 7: Method B_2 (Scheme 2). 2-[Bicyclo[2.2.1]-2-heptyl]aminodiphenylamine (7p). A mixture of 2-aminodiphenylamine **(1)** (5.0 g, 27 mmol), norcamphor (3.0 g, 27 mmol) and molecular sieves in dry toluene (200 mL) was heated to 120 °C for 6 h. The mixture was allowed to cool to room temperature, filtered and the solution concentrated in vacuo. The residue was dissolved in ethanol (200 mL), then sodium borohydride (3.0 g, 81 mmol) was added portionwise. The resulting mixture was stirred at 23 °C for 30min, then diluted with water (150 mL) and extracted with ethyl acetate (300 mL). The organic layer was washed with brine (2 × 200 mL), dried and concentrated in vacuo to an oil which was purified by flash chromatography (eluting with CH−EA 9:1) to give the title compound as a yellow oil (3.5 g, 46%): TLC $R_f = 0.47$ (CH/EA 9:1); MS (FAB) *m/e* 279 (MH^+); IR ν_{max} 3373 (NH), 1601, 1512 and 1497 (C=C) cm^{-1}; ^1H NMR δ 7.24−7.14 (m, 2H); 7.14−7.04 (m, 2H); 6.81 (t, 1H); 6.76−6.62 (m 4H); 5.04 (bs, 1H); 4.29 (bs, 1H); 3.68 (m, 1H); 2.48 (m, 1H); 2.20 (bs, 1H); 2.10 (m, 1H); 1.58−1.42 (m, 2H); 1.40−1.1 (m, 4H); 0.74 (m, 1H).

General Procedure for Preparation of Compounds of General Formula 8: Route B (Scheme 2). 2,4-Dioxo-5-*N*-(2-fluorophenyl)-1-*N*-(3-methylbut-1-yl)-3-phenylhydrazono-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (8c). The intermediate **7c** (6.3 g, 23 mmol) and the 2-phenylhydrazonomalonyl dichloride[18](6.8 g, 27.7 mmol) were each taken up in THF (150 mL) and dropped in a flask containing THF (200 mL) maintained at −5 °C under a nitrogen atmosphere. After complete addition the solution was allowed to warm to room temperature and then heated to 50 °C for 2−3 h. The solution was concentrated in vacuo to an oil, which was purified by flash chromatography (eluting with CH−EA 8:2) to give the title compound as a yellow solid (5.8 g, 57%): TLC $R_f = 0.59$ (CH/EA 7:3); IR ν_{max} 1700 (C=O) cm^{-1}; ^1H NMR δ 11.34 and 11.15 (2d, 1H); 7.7 (m., 1H); 7.5−6.9 (m, 13H); 4.58 (m, 1H); 3.65 (m, 1H); 1.8−1.5 (m, 3H); 0.95 and 0.94 (2d, 3H); 0.81 (d, 3H).

Analytical data for representative compounds are as follows.

1-*N*-(1,3-Dimethylbut-1-yl)-2,4-dioxo-5-*N*-phenyl-3-phenylhydrazono-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (8d): TLC $R_f = 073$ (CH/EA 7:3); MS (FAB) *m/e* 441 (MH^+); IR ν_{max} 1668, 1653 (C=O), 1591 (C=C) cm^{-1}; ^1H NMR δ 11.21, 10.96, 10.95 (3bs, 1H); 7.52−6.93 (m, 14H); 4.06, 4.31 (2m, 1H); 1.8−1.4 (m, 3H); 1.72, 1.72, 1.70, 1.61 (4d, 3H); 1.01−0.85 (d, 6H).

1-*N*-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-*N*-(2-fluorophenyl)-3-phenylhydrazono-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (8g): mp 112−114 °C; TLC $R_f = 0.40$ (CH/EA 8:2); MS (FAB) *m/e* 459 (MH^+); IR ν_{max} 1670 and 1653 (C=O) cm^{-1}; ^1H NMR δ 11.31 and 11.14 (2bs, 1H); 7.72 (dt, 1H); 7.54−6.88 (m, 12H); 4.66−4.48 (m, 1H); 3.64−3.56 (m, 1H); 1.6−1.5 (m, 2H); 0.99 (s, 9H).

1-*N*-(3-Cyclopentylpropen-2-yl)-2,4-dioxo-5-*N*-phenyl-3-phenylhydrazono-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (8h): TLC $R_f = 0.75$ (CH/EA 3:1); IR ν_{max} 3300 (NH); 1666 (C=O); 1637−1591 (C=C) and (C=N) cm^{-1}; ^1H NMR δ 11.20 and 10.94 (bs, 1H); 7.60−6.80 (m, 14 H); 4.56 and 4.30 (m, 1H); 2.60 (m, 1H); 2.05−1.1 (m, 13H).

1-*N*-(2-Cyclopentylethyl)-2,4-dioxo-5-*N*-(2-fluorophenyl)-3-phenylhydrazono-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (8i): TLC $R_f = 0.71$ (CH/EA, 1:1); mp 147−50 °C; IR ν_{max} 3250 (NH); 1670−1659 (C=O), 1610−1595 (C=C) cm^{-1}; ^1H NMR δ 11.33−11.31 (bs, 1H); 7.70−6.88 (m, 13H); 4.68−4.50 (m, 2H); 3.78−3.6 (m, 2H); 1.90−1.1 (m, 9H).

1-(Adamant-1-methyl)-2,4-dioxo-5-phenyl-3-phenylhydrazono-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (8m): 93%; TLC $R_f = 0.39$ (CH/EA, 8:2); MS (FAB) *m/e* 505 (MH^+); IR ν_{max} 1732 (C=O), 1663, 1637, 1601 (C=C) and (C=N) cm^{-1}; ^1H NMR δ 11.24 and 11.21 (2bs, 1H); 7.60−6.88 (m, 14 H); 4.74 and 4.62 (2d, 1H); 3.35 (d, 1H); 1.94 (m, 3H); 1.74−1.46 (m, 12H).

1-(Adamant-2-yl)-2,4-dioxo-5-phenyl-3-phenylhydrazono-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (8o): TLC $R_f = 060$ (CH/EA 80:20); IR ν_{max} 1664 and 1632 (C=O), 1589 (C=C) cm^{-1}; ^1H NMR δ 12.41 and, 11.21 (2s, 1H); 7.54−6.88 (m, 14H); 4.50 and 4.42 (2m 1H); 3.12 and 2.93 (2m, 1H); 2.30−2.20 (m, 1H); 2.06−1.26 (m, 12H).

1-[Bicyclo[2.2.1]-2-heptyl]-2,4-dioxo-5-phenyl-3-phenylhydrazono-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (8p): mp 110−111 °C; TLC $R_f = 0.72$ (CH/EA, 7:3); MS (FAB) *m/e* 451 (MH^+); IR ν_{max} 1668 (C=O), 1639 and 1591 (C=C) cm^{-1}; ^1H NMR δ 12.33, 12.13, 11.38, 11.28 (4 bs, 1H); 7.58−

6.9 (m, 14H); 4.63 and 4.4 (2m, 1H); 3.44 and 3.26 (m, 1H); 2.6 and 2.5 (m, 1H); 2.6−1.8 (m, 8H).

1-*N*-(Adamant-2-ylmethyl)-2,4-dioxo-5-*N*-phenyl-3-phenylhydrazono-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (8q): mp 135−6 °C dec; TLC R_f = 0.48 (CH/EA, 8:2); MS (FAB) *m/e* 505 (MH^+); IR ν_{max} 1736 and 1668 (C=O), 1653 and 1600 (C=C) cm^{-1}; ^1H NMR δ 11.27 and 11.24 (2bs, 1H); 7.5−6.9 (m, 14H); 5.12−5.04 and 5.02−4.94 (2dd, 1H); 3.67−3.61 (dd, 1H); 2.1−1.5 (m, 15H).

General Procedure for Preparation of Compounds of General Formula 5 Using Zn/AcOH: Route B (Scheme 2). 3-Amino-2,4-dioxo-5-*N*-(2-fluorophenyl)-1-*N*-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5c). A solution of the intermediate **8c** (5.8 g, 13 mmol) in glacial acetic acid (70 mL) was added, dropwise, to a suspension of zinc dust (6.37 g, 97.5 mmol) in glacial acetic acid (20 mL) cooled to 0 °C. The mixture was stirred at 23 °C for 3 h, then diluted with water (200 mL) and decanted from zinc. Solid sodium carbonate was added until pH = 9 and the mixture extracted with ethyl acetate (2 × 300 mL). The combined organic extracts were washed with brine (300 mL), dried and concentrated in vacuo to an oil which was purified by flash chromatography (eluting in gradient from CH−EA 2:1 to EA) to give compound **5c** as a white solid (2.8 g): mp 125−6 °C; TLC R_f = 0.38 (MC/MeOH, 30:1); MS (FAB) *m/e* 356 (MH^+); IR ν_{max} 1709 and 1672 (C=O), 1599 (C=C) cm^{-1}; ^1H NMR δ 7.46−7.14 (m, 7H); 6.94 (dd, 1H); 4.48 (m, 1H); 4.28 (s, 1H); 3.71 (m, 1H); 1.59 (m, 1H); 1.50 (m, 2H); 0.92 (d, 3H); 0.91 (d, 3H).

Analytical data for representative compounds are as follows.

3-Amino-1-*N*-(1,3-dimethylbut-1-yl)-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5d): TLC R_f = 0.53 (MC/MeOH, 9:1); MS (FAB) *m/e* 352 (MH^+); IR ν_{max} 3500−3000 (NH_2), 1703 and 1672 (C=O), 1593 (C=C) cm^{-1}; ^1H NMR δ 7.46−7.36 (m, 3H); 7.36−7.14 (m, 5H); 6.95 (dt, 1H); 4.5−4.3 (m, 1H); 4.42−4.39 (m, 1H); 2.11−1.7 (m, 1H); 1.64−1.44 (m, 2H); 1.57−1.55 (d, 3H); 0.92−0.83 (4d, 6H).

3-Amino-1-*N*-(3,3-dimethylbut-1-yl)-2,4-dioxo-5-*N*-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5f): mp 98−100 °C; TLC R_f = 0.30 (MC/MeOH); MS (FAB) *m/e* 370 (MH^+); IR ν_{max} 3371−3314 (NH); 1701 and 1670 (C=O), 1593 (C=C) cm^{-1}; ^1H NMR δ [[7.42 (dd); 7.4−7.3 (m); 7.32 (dt)] 13H]; 7.26−7.12 [[(m); 7.18 (dt)] 3H]; 6.96 (dd, 1H); 4.50−4.40 (m, 1H); 4.36 (s, 1H); 3.76−3.66 (m, 1H); 2.47 (bs, 2H); 1.50 (m, 2H); 0.95 (s, 9H).

3-Amino-1-*N*-(3-cyclopentylprop-2-yl)-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5h): TLC R_f = 0.80 (MC/MeOH, 9:1); IR ν_{max} 3366−3200 (NH_2), 1699 and 1663(C=O), 1591 (C=C) cm^{-1}; ^1H NMR δ 7.48 7.12 (m, 8H); 6.98 and 6.90 (2dd, 1H); 4.46−4.36 and 4.58−4.50 (2m, 1H); 4.20 and 4.18 (s, 1H); 2.30−2.20 (m, 1H); 2.00−1.10 (m, 10H); 1.57 and 1.45 (2d, 3H).

3-Amino-1-*N*-(2-cyclopentylethyl)-2,4-dioxo-5-*N*-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5i): TLC R_f = 0.63 (MC/MeOH, 9:1); IR ν_{max} 1709 and 1672 (C=O), 1597 (C=C) cm^{-1}; ^1H NMR δ 7.44 (dd, 1H); 7.42−7.28 (m, 3H); 7.26−7.14 (m, 3H); 6.95 (dd, 1H); 4.45 (m, 1H); 3.71(m, 1H); 4.29(s, 1H); 2.20−1.90 (bs, 2H); 1.86−1.68 (m, 3H); 1.68−1.42 (m, 6H); 1.20−1.04 (m,2H).

1-*N*-(Adamant-2-yl)-3-amino-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5o): mp 231−3 °C dec; TLC R_f = 0.61 (MC/MeOH, 9:1); IR ν_{max} 3379 (NH_2), 1697 and 1663 (C=O), 1591 (C=C) cm^{-1}; ^1H NMR δ 7.46−7.20 (m, 8H); 7.0−6.9 (m, 1H); 4.52 (bs, 1H); 4.24 (s, 1H); 2.96 (bs, 1H); 2.33 (bs, 1H); 2.2−1.1 (m, 14H).

3-Amino-1-*N*-[bicyclo[2.2.1]hept-2-yl]-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5p): mp 172−3 °C; TLC R_f = 0.30 (EA/MeOH, 95:5); MS (FAB) *m/e* 362 (MH^+); IR ν_{max} 1691 and 1666 (C=O), 1595 (C=C) cm^{-1}; ^1H NMR δ 7.5−7.1 (m, 8H); 6.98 and 6.95 (2dd, 1H); 4.50−4.42 (m, 1H); 4.27 (s, 1H); 3.49 and 2.66 (2m, 1H); 2.5 and 1.96 (2m, 2H); 2.40 and 1.64 (2bs, 2H); 2.28 and 2.18 (2t, 1H); [1.56−1.4, 1.4−1.1, 1.02, 0.86 (4m, 7H)].

1-*N*-(Adamant-2-ylmethyl)-3-amino-2,4-dioxo-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5q): mp 209−210 °C; TLC R_f = 0.38 (EA/MeOH, 20:1); MS (FAB) *m/e* 416 (MH^+) IR ν_{max} 1697 and 1664 (C=O) cm^{-1};^1H NMR δ 7.5−7.15 (m, 8H); 6.94 (dd, 1H); 5.06 (dd, 1H); 4.27 (s, 1H); 3.60 (dd, 1H); 2.3−1.5 (m, 15H).

General Procedure for Preparation of Compounds of General Formula 5 Using Catalic Hydrogenation: Route B (Scheme 2). 1-*N*-(Adamant-1-ylmethyl)-3-amino-2,4-dioxo-5-*N*-phenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (5m). 10% Pd/C (1.51 g) and concentrated hydrochloric acid (10 mL) were added to a solution of the intermediate **8m** (3.01 g, 5.96 mmol) in methanol (100 mL) and the mixture was hydrogenated at 1 atm. for 8 h. The catalyst was filtered over Celite and the filtrate concentrated in vacuo. The residue was dissolved in ethyl acetate (200 mL), washed with a 10% sodium hydroxide solution (3 × 100 mL), water (100 mL) and brine (2 × 100 mL), dried and concentrated in vacuo. Purification by flash chromatography (eluting with EA−MeOH 95:5) gave the title compound as a white foam (1.92 g, 4.62 mmol, 78%).

General Procedure To Obtain Compounds of General Formula 9 (Scheme 3). 1-*N*-(Adamant-2-yl)-2,4-dioxo-3-isocyanato-5-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (9o). Phosgene in toluene (1.93 M solution, 10 mL) was added to a solution of the intermediate **5** (0.285 g, 0.68 mmol) in dichloromethane (10 mL). The resulting solution was stirred at 23 °C for 4 h, then concentrated in vacuo at 50 °C for 2.5 h to give the title compound as a white foam (0.29 g, 0.67 mmol, 98%): IR ν_{max} 2220 (N=C), 1697 and 1676 (C=O) cm^{-1}; ^1H NMR δ 7.50−7.15 (m, 8H); 7.05−6.95(m, 1H); 4.7 (s, 1H); 4.55 (m, 1H); 3.05 (m, 1H); 2.35 (m, 1H); 1.95−1.1 (m, 12H).

Analytical data for representative compounds are as follows.

2,4-Dioxo-5-*N*-(2-fluorophenyl)-3-isocyanato-1-*N*-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (9c): mp 167−8 °C; IR ν_{max} 2243 (C=N=O), 1717 and 1684 (C=O), 1601 (C=C) cm^{-1}; ^1H NMR δ 7.46 (dd, 1H); 7.44−7.32 (m, 2H); 7.3−7.15 (m, 4H); 7.0 (dd, 1H); 4.64 (s, 1H); 4.52−4.4 (m, 1H); 3.8−3.68 (m, 1H); 1.7−1.45 (m, 3H); 0.94 (d, 3H); 0.91 (d, 3H).

1-(3,3-Dimethylbutyl)-2,4-dioxo-3-isocyanato-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (9f): mp 205−7 °C; IR ν_{max} 2218 (N=C=O); 1693 and 1668 (C=O) cm^{-1}; ^1H NMR δ 7.48−7.18 (m, 8H); 7.01 (dd, 1H); 4.57 (s, 1H); 4.54−4.42 (m, 1H); 3.80−3.68 (m, 1H); 1.60−1.46 (m, 2H); 0.96 (s, 9H).

1-(2-Cyclopentylethyl)-2,4-dioxo-5-(2-fluorophenyl)-3-isocyanato-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (9i): TLC R_f = 0.63 (MC/MeOH, 9:1); IR ν_{max} 2232 (N=C), 1715−1670 (C=O) cm^{-1}; ^1H NMR δ 7.46 (dd, 1H); 7.44−7.15 (m, 6H); 7.00 (dd, 1H); 4.63 (s, 1H); 4.44 (m, 1H); 3.75 (m,1H); 1.86−1.4 (m, 9H); 1.20−1.06 (m, 2H).

General Procedure To Obtain Compounds of General Formula 10 (Scheme 3). 2,4-Dioxo-5-*N*-(2-fluorophenyl)-1-*N*-(3-methylbut-1-yl)-3-(phenyloxycarbonylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (10c). Pyridine (0.137 mL, 1.7 mmol) and phenyl chloroformate (0.21 mL, 1.7 mmol) were added to a solution of the intermediate **7c** (0.3 g, 0.85 mmol) in dichloromethane (15 mL) under a nitrogen atmosphere. The resulting solution was stirred at 23 °C for 30 min, then washed with a 1% solution of hydrochloric acid (15 mL), a 5% solution of sodium hydrogen carbonate (15 mL) and brine (20 mL). The organic layer was dried and concentrated in vacuo to a solid which was triturated with ethyl acetate to give the title compound as a white solid (0.3 g, 74%): mp 226−7 °C; TLC R_f = 075 (CH/EA, 1:1); $C_{27}H_{26}FN_3O_4$; MS (FAB) *m/e* 476 (MH^+); IR (Nujol) ν_{max} 3275 (NH), 1734, 1707 and 1684 (C=O), 1593 (C=C) cm^{-1}; ^1H NMR δ 7.46 (dd, 1H); 7.44−7.14 (m, 11H); 7.00 (dd, 1H); 6.46 (d, 1H); 5.17 (d, 1H); 4.55−4.47 (m, 1H); 3.77−3.68 (m, 1H); 1.6 (m, 1H); 1.56−1.46 (m, 2H); 0.94 (d, 3H); 0.92 (d, 3H).

Analytical data for representative compounds are as follows

1-*N*-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-*N*-phenyl-3-(phenyloxycarbonylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodi-

azepine (10f): mp 170−2 °C; TLC R_f = 0.80 (CH/EA, 1:1); MS (FAB) *m/e* 472 (MH^+); IR ν_{max} 3250 (NH), 1736 and 1695 (C=O), cm^{-1}; ^1H NMR δ 7.46−7.14 (m, 13H); 7.10 (dd, 1H); 6.46 (d, 1H); 5.12 (d, 1H); 4.94 (m, 1H); 3.71 (m, 1H); 1.50 (m, 2H); 0.95 (s, 9H).

1-*N*-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-*N*-(2-fluorophenyl)-3-(phenyloxycarbonylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (10g): mp 199−200 °C; TLC R_f = 0.82 (CH/EA, 1:1); MS (FAB)*m/e* 490 (MH^+); IR (Nujol) ν_{max} 3290 (NH), 1740, 1707 and 1686 (C=O), 1593 (C=C) cm^{-1}; ^1H NMR δ 7.5−7.1 (m, 12H); 7.00 (dd, 1H); 6.45 (d, 1H); 5.17 (d, 1H); 4.48−4.41 (m, 1H); 3.78−3.71 (m, 1H); 1.52 (m, 2H); 0.96 (d, 9H).

1-*N*-(2-Cyclopentylethyl)-2,4-dioxo-5-*N*-(2-fluorophenyl)-3-(phenyloxycarbonylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (10i): mp 205−7 °C; TLC R_f = 0.68 (CH/EA, 1:1); MS (FAB) *m/e* 502 (MH^+); IR ν_{max} 3280 (NH), 1736, 1709 and 1682 (C=O) cm^{-1}; ^1H NMR δ 7.46 (dd, 1H); 7.44−7.28 (m, 5H); 7.28−7.08 (m, 6H); 6.99 (dd, 1H); 6.46 (d, 1H); 5.17 (d, 1H); 4.47 (m, 1H); 3.72(m, 1H); 1.86−1.70(m, 3H); 1.70−1.44 (m, 6H); 1.12 (m, 2H).

1-*N*-(2-Adamantyl-1-ylethyl)-2,4-dioxo-5-*N*-phenyl-3-(phenyloxycarbonylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (10n): TLC R_f = 0.77 (CH/EA, 1:1); IR ν_{max} 1742, 1707 and 1674 (C=O) cm^{-1}; ^1H NMR δ 7.43 (t, 3H); 7.38−7.30 (m, 4H); 7.25−7.14 (m, 5H); 6.99 (dd, IH); 6.46 (d, 1H); 5.06 (d, 1H); 4.51 (m, 1H); 3.72 (m, 1H); 1.966 (bs, 3H); 1.67 (bq, 6H); 1.54 (d, 6H); 1.36 (2d, 2H).

General Procedure To Obtain Compounds of General Formula I Directly from Amines 5 (Scheme 3). *N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′- phenylurea (23). Phenyl isocyanate (0.033 mL, 0.25 mmol) was added to a solution of the intermediate **6o** (0.1 g, 0.24 mmol) in dichloromethane (5 mL) under a nitrogen atmosphere. The mixture was stirred at 23 °C for 1 h, then concentrated in vacuo. The residue was triturated with acetonitrile to give compound **23** (0.112 g, 0.21 mmol, 87%) as a white solid: mp 194−6 °C; TLC R_f = 0.77 (CH/EA 1:1); $C_{33}H_{34}N_4O_3$ $1H_2O$; MS (FAB) *m/e* 535 (MH^+); IR ν_{max} 3294 (NH), 1717, 1705 and 1680 (C=O); 1643 (C=C) cm^{-1}; ^1H NMR δ 7.5−6.96 (m, 14H); 7.08 (bs, 1H); 6.50 (d, 1H); 5.31 (d, 1H); 4.49 (d, 1H); 3.37 (d, 1H); 1.84 (m, 3H); 1.6−1.3 (m, 12H).

Analytical data for representative compounds are as follows.

***N*-[1-Butyl-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (11):** TLC R_f = 0.65 (MC/MeOH, 95:5); $C_{26}H_{26}N_4O_3$; MS (FAB) *m/e* 443 (MH^+); IR ν_{max} 3431 (NH); 1707−1670 (C=O), 1599 (C=C) cm^{-1}; ^1H NMR δ 7.40−7.00 (m, 14H); 6.66 (bs, 1H); 6.22 (d, 1H); 5.3 (d, 1H); 4.55 (m, 1H); 3.70 (m, 1H); 1.53 (m, 2H); 1.3 (m, 2H); 0.88 (t, 3H).

***N*-[2,4-Dioxo-5-phenyl-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (12):** TLC R_f = 0.87 (MC/MeOH, 95:5); $C_{27}H_{28}N_4O_3$; MS (FAB) *m/e* 457 (MH^+); IR ν_{max} 3440−3350 (NH), 1701 and 1680 (C=O), 1616 and 1599 (C=C) cm^{-1}; ^1H NMR δ 7.44−7.16 (m, 14H); 7.00 (m, 1H); 6.4 (bs, 1H); 5.33 (d, 1H); 4.53 (m, 1H); 3.68 (m 1H); 1.6−1.4 (m, 3H); 0.89 (d, 3H); 0.86 (d, 3H).

(+)-*N*-[2,4-Dioxo-5-phenyl-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (13): mp >254 °C; TLC R_f = 0.87 (MC/MeOH, 95:5); $[\alpha]_D$ = +116 (CH_2Cl_2 *c* = 8.48 mg/mL); $C_{27}H_{28}N_4O_3$; MS (FAB) *m/e* 457 (MH^+); for IR and ^1H NMR data see compound **12**.

(−)-*N*-[2,4-Dioxo-5-phenyl-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (14): TLC R_f = 0.87 (MC/MeOH, 95:5); $[\alpha]_D$ = −104.88 (CH_2Cl_2 *c* = 5.035 mg/mL); TLC R_f = 0.87 (MC/MeOH, 95:95); $C_{27}H_{28}N_4O_3$; MS (FAB) *m/e* 457 (MH^+); for IR and ^1H NMR data see compound **12**.

***N*-[2,4-Dioxo-5-(2-fluorophenyl)-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (15):** mp 254−5 °C; TLC R_f = 0.65 (CH/EA, 1:1); $C_{27}H_{27}FN_4O_3$; MS (FAB) *m/e* 475 (MH^+); IR ν_{max} 3450 (NH), 1707 and 1670 (C=O), 1601 and 1533 (C=C) cm^{-1}; ^1H NMR δ 7.46 (dd, 1H); 7.4−7.1 (m, 10H); 7.03 (m, 1H); 6.99 (dd, 1H); 6.93 (bs, 1H); 6.35 (d, 1H); 5.37 (d, 1H); 4.46 (m, 1H); 3.70 (m, 1H); 1.6−1.4 (m, 3H); 0.90 (d, 3H); 0.89 (d, 3H).

***N*-[1-(1,3-Dimethylbut-1-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (16):** TLC R_f = 0.53 (CH/EA, 1:1); $C_{28}H_{30}N_4O_3$; MS (FAB) *m/e* 471 (MH^+); IR ν_{max} 3370 (NH), 1701 and 1670 (C=O), 1651 and 1601 (C=C) cm^{-1}; ^1H NMR δ 7.44−7.35 (m, 3H); 7.34−7.24 (m, 2H); 7.24−7.15 (m, 8H); 6.98 (m, 2H); 6.54 and 6.53 (2d, 1H); 5.33 and 5.32 (2d, 1H); 4.58 and 4.44 (mq +q, 1H); 2.11 and 1.74−1.64 (2m, 1H); 1.64−1.44 (m, 2H); 1.54,1.44 (2d, 3H); 0.89, 0.88, 0.87, 0.83 (4d, 6H).

***N*-[1-(2,3-Dimethylbut-1-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (17):** TLC R_f = 0.49 (CH/EA, 1:1); $C_{28}H_{30}N_4O_3$; MS (FAB) *m/e* 471 (MH^+); IR ν_{max} 3300 (NH), 1707 and 1641 (C=O); 1558 and 1541 (C=C) cm^{-1}; ^1H NMR δ 7.46−7.10 (m, 11H); 6.9 (m, 4H); 6.4 (2d, 1H,); 5.32 and 5.29 (2d, 1H); 4.61 and 4.48 (2dd, 1H); 3.60 and 3.42 (2dd, 1H); 1.8 (m, 1H); 1.4 (m, 1H); 0.86 and 0.80 (2d, 3H); 0.77 and 0.75 (2d, 3H); 0.73 and 0.70 (2d, 3H).

***N*-[1-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (18):** mp 236 °C; TLC R_f = 0.57 (CH/EA, 1:1); $C_{28}H_{30}N_4O_3$; MS (FAB) *m/e* 471 (MH^+); IR ν_{max} 3431−3350 (NH), 1705−1668 (C=O), 1599 (C=C) cm^{-1}; ^1H NMR δ 7.48−7.16 (m, 13H); 7.04−6.96 (m, 2H); 6.52 (d, 1H); 5.35 (d, 1H); 4.51−4.40 (m, 1H); 3.73−3.63 (m, 1H); 1.47 (t, 2H); 0.92 (s, 9H).

***N*-[1-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (19):** mp 271−2 °C; TLC R_f = 0.32 (CH/EA, 7:3); $C_{28}H_{29}FN_4O_3$; MS (FAB) *m/e* 489 (MH^+); IR ν_{max} 3310 (NH), 1718, 1668 and 1639 (C=O), 1601 and 1556 (C=C) cm^{-1}; ^1H −NMR δ [[7.45 (dd); 7.4−7.10 (m), 11H]; 7.06−6.97 (m, 3H); 6.41 (d, 1H); 5.36 (d, 1H); 4.48−4.37 (m, 1H); 3.76−3.66 (m 1H); 1.50 (m, 2H); 0.92 (s, 9H).

***N*-[1-(Cyclopentylprop-2-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (20):** TLC R_f = 0.51 (CH/EA, 1:1); $C_{30}H_{32}N_4O_3$; MS (FAB) *m/e* 497 (MH^+); IR ν_{max}3400−3300 (NH), 1701 and 1670 (C=O), 1651 and 1597 (C=C) cm^{-1}; ^1H NMR δ 7.50−7.00 (m, 13H); 6.90 (2m, 1H); 6.4 (m, 1H); 5.29 (d, 1H); 4.60−4.50 and 4.50−4.40 (2m, 1H); 2.20−1.10 (m, 11H); 1.42 (d, 3H).

***N*-[1-(2-Cyclopentylethyl)-2,4-dioxo-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (21):** mp 255−7 °C; TLC R_f = 0.58 (CH/EA, 1:1); $C_{29}H_{29}FN_4O_3$; MS (FAB) *m/e* 501 (MH^+); IR ν_{max} 3400 (NH), 1718 and 1650 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR δ 7.46 (dd, 1H); 7.4−7.1 (m, 11H); 7.0 (t, 1H); 6.98 (d, 1H); 6.52 (d, 1H); 5.38 (d, 1H); 4.44 (m, 1H); 3.66 (m, 1H); 1.84−1.40 (m, 9H); 1.20−1.00 (m, 2H).

***N*-[2,4-Dioxo-5-phenyl-1-(2-phenylethyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (22):** TLC R_f = 0.45 (CH/EA, 1:1); $C_{30}H_{26}N_4O_3$; MS (FAB) *m/e* 491 (MH^+); IR ν_{max} 3310 (NH), 1707 and 1678 (C=O), 1643, 1603 and 1556 (C=C) cm^{-1}; ^1H NMR δ 7.43 (dd, 1H), 7.36−7.12 (m, 14H); 7.07−6.94 (m, 4H); 6.48 (d, 1H); 5.36 (d, 1H); 4.78−4.66 (m, 1H); 3.98−3.86 (m, 1H); 2.92 (m, 2H).

***N*-(+)-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (24):** mp 265−6 °C; TLC R_f = 0.77 (CH/EA 1:1); $[\alpha]_D$ = +42.5 ($CHCl_3$ *c* = 10.05 mg/mL); $C_{33}H_{34}N_4O_3$; MS (FAB) *m/e* 535 (MH^+); for IR and ^1H NMR data see compound **23**.

***N*-(−)-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (25):** 75%; mp 265−6 °C; TLC R_f = 0.77 (CH/EA, 1:1); $[\alpha]_D$ = −39.4 (CH_2Cl_2 *c* = 6.08 mg/mL); $C_{33}H_{34}N_4O_3$; MS (FAB) *m/e* 535 (MH^+); for IR and ^1H NMR data see compound **23**.

***N*-[1-(2-Adamant-1-ylethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (26):** TLC R_f = 0.55 (CH/EA, 1:1); MS (FAB) *m/e* 549 (MH^+); $C_{34}H_{37}N_4O_3$; IR ν_{max} 3312 (NH), 1701, 1668 and 1645 (C=O), 1601 and 1580 (C=C) cm^{-1}; ^1H NMR δ 7.46−7.14 (m, 12H); 7.02−6.96 (m, 3H); 6.56 (d, 1H); 5.35 (d, 1H); 4.45 (m, 1H); 3.70 (m, 1H); 1.93−1.28 (m, 17H).

***N*-[1-(Adamant-2-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (27):** mp 191−4 °C; TLC R_f = 0.76 (CH/EA, 1:1); $C_{32}H_{32}N_4O_3$; MS (FAB) *m/e* 521 (MH^+); IR ν_{max} 3306 (NH), 1713 and 1705 (C=O), 1641 and 1601 (C=C) cm^{-1}; ^1H NMR δ 7.44−7.20 (m, 13H); 7.08 (m, 1H); 7.02−6.9 (m, 1H); 6.39 (d, 1H); 5.34 (d, 1H); 4.50 (m, 1H); 2.95 (m, 1H); 2.32 (m, 1H); 1.9−1.1 (m, 11H).

***N*-[1-[Bicyclo[2.2.1]hept-2-yl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (28):** mp 267−8 °C; TLC R_f = 0.62 (CH/EA, 1:1); $C_{29}H_{28}N_4O_4$; MS (FAB) *m/e* 481 (MH^+); IR ν_{max} 3300 (NH), 1705, 1678 and 1645 (C=O), 1599 and 1556 (C=C) cm^{-1}; ^1H NMR δ [[7.46−7.12 (m); 7.03−6.94 (m)] 15H]; 6.42 and 6.44 (2d, 1H); 5.33 and 5.32 (2d, 1H); 4.5−4.4 (m, 1H); 3.46 and 2.64 (2s, 1H); 2.18 (m, 1H); 2.40 and 1.96 (2m, 1H); [[1.6 (m); 1.54−1.38 (m); 1.38−1.1 (m); 0.99 (m); 0.86 (m), 7H].

***N*-[1-(Adamant-2-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-phenylurea (29):** mp 192−3 °C; TLC R_f = 0.73 (CH/EA, 1:1); $C_{29}H_{28}N_4O_4$; MS (FAB) *m/e* 535 (MH^+); IR ν_{max} 3306 (NH), 1717 and 1701 (C=O), 1643 and 1620 (C=C) cm^{-1}; ^1H NMR δ 7.5−7.14 (m, 12H); 7.00 (dd+t, 2H); 7.05 (bs, 1H); 6.47 (d, 1H); 5.33 (d, 1H); 5.05 (dd, 1H); 3.59 (dd, 1H); 2.02 (m, 1H); 1.84−1.36 (m, 14H).

***N*-[2,4-Dioxo-5-(2-fluorophenyl)-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(*N*,*N*-dimethylamino)phenyl]urea (30):**[44] mp 252−3 °C; TLC R_f = 0.50 (CH/EA, 1:1); $C_{29}H_{32}FN_5O_3$; MS (FAB) *m/e* 518 (MH^+); IR (Nujol) ν_{max} 3312 (NH), 1707,1676 and 1639 (C=O), 1593 and 1558 (C=C) cm^{-1}; ^1H NMR δ 7.45 (dd, 1H); 7.41−7.28 (m, 2H); 7.25−7.1 (m, 5H); 7.134 (t 1H); 6.98 (dd, 1H); 6.82 (t, 1H); 6.63 (s, 1H); 6.60 (dd, 1H); 6.46 (dd, 1H); 6.36 (d, 1H); 5.36 (d, 1H); 4.51−4.41 (m, 1H); 3.74−3.64 (m, 1H); 2.92 (s, 6H); 1.6−1.42 (m, 3H); 0.91 (d, 3H); 0.90 (d, 3H).

(+)-*N*-[2,4-Dioxo-5-(2-fluorophenyl)-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(*N*,*N*-dimethylamino)phenyl]urea (31):[44] mp 252−3 °C; TLC R_f = 0.50 (CH/EA, 1:1); $[\alpha]_D$ = +109.6 (CH_2Cl_2 *c* = 0.1 mg/mL); $C_{29}H_{32}FN_5O_3$; MS (FAB) *m/e* 518 (MH^+); for IR and ^1H NMR data see compound **30**.

(−)-*N*-[2,4-Dioxo-5-(2-fluorophenyl)-1-(3-methylbut-1-yl)-2,3,4,5,2-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(*N*,*N*-dimethylamino)phenyl]urea (32):[44] mp 252−3 °C; TLC R_f = 0.50 (CH/EA, 1:1); $[\alpha]_D$ = −112.3 (CH_2Cl_2 *c* = 0.7 mg/mL); $C_{29}H_{32}FN_5O_3$; MS (FAB) *m/e* 518 (MH^+); for IR and ^1H NMR data see compound **30**.

(+)-*N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-hydroxyphenyl)urea (47): TLC R_f = 0.20 (CH/EA, 2:1); $[\alpha]_D$ = +76.9 (DMSO *c* = 8.90 mg/mL); $C_{33}H_{34}N_4O_4$; MS (FAB) *m/e* 551 (MH^+); IR ν_{max} 3450−3310 (NH), 1693 and 1639 (C=O) cm^{-1}; ^1H NMR δ 9.22 (bs, 1H); 9.03 (bs, 1H); 7.82 (d, 1H); 7.48 (t, 2H); 7.38 (m, 2H); 7.29 (d, 2H); 7.27 (m, 1H); 6.97 (t, 1H); 6.94 (dd, 1H); 6.88 (t, 1H); 6.87 (d, 1H); 6.70 (d, 1H); 6.29 (dd, 1H); 4.97 (d, 1H); 4.25 (d, 1H); 3.60 (d, 1H); 1.84 (bs, 3H); 1.66−1.25(m, 12H).

***N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-methylphenyl)urea (48):** mp 213−5 °C; TLC R_f = 0.33 (CH/EA, 2:1); $C_{34}H_{36}N_4O_3$; MS (FAB) *m/e* 548 (MH^+); IR ν_{max} 3300 (NH), 1715 and 1672 (C=O), 1645 and 1616 (C=C) cm^{-1}; ^1H NMR δ 7.49 (dd, 1H); 7.45−7.35 (m); 7.35−7.25 (m, 6H); 7.21−7.15 (m, 2H); 7.14 (t, 1H); 7.03 (m, 1H); 6.99 (dd, 1H); 6.85 (m, 1H); 6.75 (s, 1H); 6.32 (d, 1H); 5.29 (d, 1H); 4.50 (d, 1H); 3.38 (d, 1H); 2.29 (s, 3H); 1.86 (s, 3H); 1.68−1.3 (m, 12H).

***N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-nitrophenyl)urea (49):** mp 244−6 °C; TLC R_f = 0.32 (CH/EA, 2:1); $C_{33}H_{33}N_5O_5$; MS (FAB) *m/e* 580 (MH^+); IR ν_{max} 3296 (NH), 1713 and 1645 (C=O), cm^{-1}; ^1H NMR δ 8.25 (bs, 1H); 8.15 (t, 1H); 7.64 (m, 1H); 7.52 (dd, 1H); 7.45 (m, 4H); 7.36−7.29 (m, 2H); 7.24−7.17 (m, 2H); 7.13 (t, 1H); 7.06 (d, 1H); 7.02 (dd, 1H); 5.27 (d, 1H); 4.51 (d, 1H); 3.40 (d, 1H); 1.86 (bs, 3H); 1.66−1.34 (m, 12H).

***N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-bromophenyl)urea (50):** mp 254−6 °C; TLC R_f = 0.53 (CH/EA, 2:1); $C_{33}H_{33}BrN_4O_3$; MS (FAB) *m/e* 416 (MH^+); IR ν_{max} 3290 (NH), 1717 and 1672 (C=O) cm^{-1}; ^1H NMR δ 7.56−7.15 (m, 10H); 7.03−6.88 (m, 2H); 6.99 (dd, 1H); 6.93 (dd, 1H); 6.73 (d, 1H); 5.29 (d, 1H); 4.49−3.38 (m, 2H); 1.83 (m 3H); 1.64−1.30 (m, 12H).

***N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-ethoxycarbonylphenyl)urea (51):** mp 246−8 °C; TLC R_f = 0.37 (CH/EA, 2:1); $C_{36}H_{38}N_4O_5$; MS (FAB) *m/e* 607 (MH^+); IR ν_{max} 1709, 1690 and 1670 (C=O) cm^{-1}; ^1H NMR δ 7.93 (t, 1H); 7.64−7.50 (m, 2H); 7.44−7.39 (m, 5H); 7.38 (bs, 1H); 7.35−7.27 (m, 2H); 7.24−7.14 (m), 6.89 (dd, 1H); 6.58 (d, 1H); 5.31 (d, 1H); 4.50 (d, 1H); 4.34 (m, 2H); 3.38 (d, 1H); 1.85 (m, 3H); 1.61−1.51 (2m, 6H); 1.45−1.37 (2m, 6H); 1.35 (t, 3H).

***N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-carboxyphenyl)urea (52).** An aqueous 0.1 M solution of lithium hydroxide (6.6 mL) was added to a solution of intermediate **51** (0.2 g, 0.33 mmol) in THF (15 mL) previously cooled to 0 °C. The solution was stirred at 23 °C for 16 h, then heated at 60 °C for 1 h and at 80 °C for 13 h. The solution was cooled to 23 °C, neutralized with acetic acid, concentrated in vacuo and the residue purified by flash chromatography (eluting in gradient from CH−EA 3:1 to MC and finally to MC−MeOH 10:1) to give compound **52** as a white solid (0.183 g), still containing traces of inorganic salts. This material was further purified by dissolution in MC and washing with 10% HCl; the organic layer was dried, concentrated in vacuo and the residue triturated with diethyl ether to give the pure title compound (0.150 g, 78%): mp 260−70 °C dec; TLC R_f = 0.64 (EA); $C_{34}H_{34}N_4O_5$; MS (FAB) *m/e* 579 (MH^+); IR ν_{max} 3383, 3319 and 3184 (NH and OH), 1760 and 1650 (C=O) cm^{-1}; ^1H NMR δ 8.34 (s, 1H); 8.31 (d, 1H); 7.84 (s, 1H); 7.69−7.63 (m, 2H); 7.52 (d, 1H); 7.47−7.16 (m, 8H); 7.03 (m, IH); 5.24 (d, 1H); 4.55 (d, 1H); 3.43 (d, 1H); 1.92 (m, 3H); 1.7−1.3 (m, 12H).

***N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(*N*,*N*-dimethylamino)phenyl]urea (53):** mp 263−5 °C; TLC R_f = 0.52 (CH/EA, 1:1); $C_{35}H_{39}N_5O_3$; MS (FAB) *m/e* 578 (MH^+); IR ν_{max} 3300 (NH), 1717 and 1674 (C=O) cm^{-1}; ^1H NMR δ 7.48 (dd, 1H); 7.45−7.24 (m, 6H); 7.19−7.10 (m, 2H); 6.98 (dd, 1H); 6.93 (dd, 1H); 6.61 (s, 1H); 6.58−6.45 (m, 2H); 6.38 (d, 1H); 5.29 (d, 1H); 4.49−3.37 (m, 2H); 2.92 (s, 6H); 1.87 (m, 3H); 1.63−1.53 (m, 6H); 1.44−1.34 (m, 6H).

(+)-*N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-hydroxymethylphenyl)urea (54): mp 204−6 °C; TLC R_f = 0.50 (CH/EA 1:2); $[\alpha]_D$ = +70.8 (*c* = 7.40 mg/mL $CHCl_3$); $C_{34}H_{36}N_4O_4$; MS (FAB) *m/e* 565 (MH^+); IR ν_{max} 3287 (NH), 1699 and 1670 (C=O), 1634 and 1560 (C=C) cm^{-1}; ^1H NMR δ 7.49 (dd, 1H); 7.44 (m, 4H); 7.24 (m, 2H); 7.22 (m, 2H); 7.12 (m, 1H); 7.40−6.96 (m, 3H); 6.46 (d, 1H); 5.27 (d, 1H); 4.57 (t, 2H); 4.50 (d, 1H); 3.38 (d, 1H); 2.8−2.2 (m, 1H); 1.89 (bs, 3H); 1.70−1.40 (m, 12H).

3-(*tert*-Butyldiphenylsilyloxymethyl)phenyl isocyanate was prepared from commercially available 3-aminobenzyl alcohol by reaction with *tert*-butyldiphenyl chlorosilane; the obtained intermediate was reacted with phosgene to give the final 3-(*tert*-butyldiphenylsilyloxymethyl)phenyl isocyanate.

(+)-*N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(morpholin-4-ylmethyl)phenyl]urea (55): mp 175−7 °C; TLC R_f = 0.38 (EA); $[\alpha]_D$ = +39.8 (*c* = 6.45 mg/mL $CHCl_3$); $C_{38}H_{43}N_5O_4$; MS (FAB) *m/e* 634 (MH^+); IR ν_{max} 3292 (NH); 1701 and 1676 (C=O) cm^{-1}; ^1H NMR δ 7.49 (dd, 1H); 7.46−7.14 (m, 10H); 7.03 (bs, 1H); 6.99 (dd, 1H); 6.74 (d, 1H); 6.25 (m, 1H); 5.28 (d, 1H); 4.49 (d, 1H); 3.69 (m, 4H); 3.43 (s, 2H); 3.38 (d, 1H); 2.42 (m, 4H); 1.87 (m, 3H); 1.70−1.30 (m, 12H).

3-(Morpholinomethyl)phenyl isocyanate was prepared according to known procedure starting from commercially available 3-chloromethylnitrobenzene.[45]

(+)-*N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-

2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(4-bromophenyl)urea (56): mp 297 °C dec; TLC R_f = 0.53 (CH/EA 2/1); $[\alpha]_D$ = +47.4 ($CHCl_3$ *c* = 10.25 mg/mL); $C_{33}H_{33}BrN_4O_3$; MS (FAB) *m/e* 615 (MH^+); IR ν_{max} 3200 (NH), 1705 and 1684 (C=O) cm^{-1}; ^1H NMR δ 7.48 (d, 1H); 7.45−7.15 (m, 9H); 7.07 (d, 2H); 7.00 (dd, 1H); 6.70 (d, 1H); 5.30 (bs, 1H); 5.28 (d, 1H); 4.49 (d, 1H); 3.37 (d, 1H); 1.84 (m, 3H); 1.66−1.3 (m, 12H).

(+)-*N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-bromophenyl)urea (57): TLC R_f = 0.53 (CH/EA, 2:1); $[\alpha]_D$ = +61.7 ($CHCl_3$ *c* = 9.60 mg/mL); $C_{33}H_{33}BrN_4O_3$; MS(FAB) *m/e* 613 (MH^+); IR ν_{max} 3300 (NH), 1709 and 1676 (C=O), 1595 (C=C) cm^{-1}; ^1H NMR δ 7.52 (bs, 1H); 7.56−7.38 (m, 4H); 7.36−7.26 (m, 4H); 7.17 (dt, 1H); 7.08−6.95 (m, 4H); 6.69 (bd, 1H); 5.27 (d, 1H); 4.50 (d, 1H); 3.39 (d, 1H); 1.86−1.3 (m, 15H).

(+)-4-[4-(Adamant-1-ylmethyl-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)ureido]phenoxy]butyric acid, ethyl ester (58): mp 255.5−6.5 °C dec; TLC R_f = 0.55 (CH/EA, 1:1); $[\alpha]_D$ = +25.7 ($CHCl_3$ *c* = 8.3 mg/mL); $C_{39}H_{44}N_4O_6$; MS (FAB) *m/e* 664 (MH^+); IR ν_{max} 3400−3333 (NH), 1736, 1699 and 1651 (C=O) cm^{-1}; ^1H NMR δ 7.48 (dd, 1H); 7.45−7.2 (m, 8H); 7.16 (tt, 1H); 6.99 (dd, 1H); 6.83 (d, 2H); 6.39 (bs, 1H); 6.1 (d, 1H); 5.25 (d, 1 H); 4.48 (d, 1H); 4.14 (q, 2H); 3.97 (t, 2H); 3.38 (d, 1H); 2.51 (t, 2H); 2.09 (m, 2H); 1.87 (m, 3H); 1.68−1.34 (m, 12H); 1.26 (t, 3H).

(+)-4-[4-(Adamant-1-ylmethyl-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)ureido]phenoxy]butyric Acid (59). Aluminum triiodide (1.656 g) was added to the solution of ethyl ester **58** (0.513 g,0.77 mmol) in dry acetonitrile (50 mL). The reaction mixture was stirred at reflux for 2 h, then concentrated in vacuo and the residue dissolved in MC (100 mL) and washed with 10% hydrochloric acid solution (80 mL), 5% sodium hydrogen carbonate solution, 10% hydrochloric acid solution (80 mL), water (2 × 80 mL), brine (2 × 80 mL) 5% sodium sodium dithionite (2 × 80 mL) and brine (2 × 80 mL). The organic extracts were dried and concentrated in vacuo and the residue purified by flash chromatography (eluting with CH−EA 3:2, then with MC−MeOH 9:10) to give the title compound as a white solid (0.182 g, 0.28 mmol): mp 195−205 °C dec; TLC R_f = 0.39 (EA); $[\alpha]_D$ = 35.6 ($CHCl_3$ *c* = 8.55 mg/mL); $C_{37}H_{40}N_4O_6$; MS (FAB) *m/e* 637 (MH^+); IR ν_{max} 3281 (NH and OH), 1695 and 1668 (C=O) cm^{-1}; ^1H NMR δ 12.1 (m, 1H); 8.96 (s, 1H); 7.82 (m, 1H); 7.49 (t, 2H); 7.37 (m, 2H); 7.28 (m, 3H); 7.22 (d, 2H); 6.94 (dd, 1H); 6.79 (d, 3H); 4.98 (d, 1H); 4.28 (d, 1H); 3.88 (t, 2H); 3.60 (d, 1H); 2.32 (t, 2H); 1.87 (m, 2H); 1.84 1.22 (m, 15H).

Continuing elution with MC−MeOH 4:1 a pure sample of **(+)-*N*-[1-(adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(4-hydroxyphenyl)urea (60)** was isolated and characterized: $[\alpha]_D$ = +35.6 ($CHCl_3$ *c* = 8.6 mg/mL); $C_{33}H_{34}N_4O_4$; MS (FAB) *m/e* 551(MH^+); IR ν_{max} 3306 (OH), 3198 (NH), 1703 and 1670 (C=O) cm^{-1}; ^1H NMR δ 7.47 (dd, 1H); 7.42−7.23 (m, 6H); 7.15 (td, 1H); 7.05 (d, 2H); 6.99 (dd, 1H); 6.94 (bs, 1H); 6.62 (s, 2H); 6.42 (bd, 1H); 6.25 (bs, 1H); 5.27 (d, 1H); 4.47 (d, 1H); 3.38 (d, 1H); 1.87 (s, 3H); 1.70−1.20 (m, 12H).

(+)-*N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(2-morpholin-4-ylethoxy)carbonyl]phenylurea (61). To a solution of (+)-1-adamant-1-ylmethyl-2,4-dioxo-3-(3-hydroxycarbonylphenyl)aminoarbonylamino-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (0.10 g) in dry THF (5 mL) *N*,*N*′-carbonyldiimidazole (0.056 g) was added and the reaction mixture was stirred at 20 °C for 20 h. The solvent was evaporated and the residue taken up in toluene; *N*-(2-hydroxyethyl)morpholine (0.069 g) was then added and stirring was continued for 16h at 20 °C and at reflux for 4 h. The reaction mixture was dried, concentrated in vacuo and the residue was taken up with MC (50 mL) and washed with saturated ammonium chloride solution (30 mL) and brine (2 × 40 mL) to give a crude compound (0.15 g) which was purified by preparative TLC using CH/MeOH 95/0.5 as eluant to give the title compound as a white solid (0.030 g, 0.43 mmol): TLC R_f = 0.2 (CH/EA, 2:1); HPLC t_R = 5.2 min (Pirkle DNBPG S5, *n*-hexane/THF 45/55); $C_{40}H_{45}N_5O_6$; MS (FAB) *m/e* 692 (MH^+); IR ν_{max} 3400 (NH), 1718 (C=O) cm^{-1}; ^1H NMR δ 7.91 (bs, 1H); 7.58 (d, 1H); 7.54−7.06 (m, 11H); 7.00 (dd, 1H); 6.65 (m, 1H); 5.27 (m, 1H); 4.54−4.38 (m, 3H); 3.73 (t, 4H); 3.38 (d, 1H); 2.79 (t, 2H); 2.61 (m, 4H); 1.87 (m); 2.2−1.3 (m, 15H).

(+)-*N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-aminophenyl)urea (62). 5% Pd/C (0.30 g) was added to a solution of (+)-(1-adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-nitrophenyl)urea (1.0 g 1.72 mmol) in dry THF (50 mL) and EtOH (50 mL) under a nitrogen atmosphere. The mixture was hydrogenated at 23 °C and 1 atm for for 2 h, then filtered and concentrated in vacuo. The residue was purified by flash chromatography (eluting with CH/EA 9/1) to give the title compound as a white solid (0.67 g, 1.22 mmol): mp 188−90 °C; TLC R_f = 0.44 (EA/MeOH, 3/1); $[\alpha]_D$ = +38.3 ($CHCl_3$ *c* = 9.65 mg/mL); $C_{33}H_{35}N_5O_3$; MS (FAB) *m/e* 550 (MH^+); IR ν_{max} 3356 (NH), 1707, 1674 and 1639 (C=O) cm^{-1}; ^1H NMR δ 7.5−7.24 (m, 7H); 7.15 (t, 1H); 7.00 (t, 2H); 6.85 (bs, 1H); 6.82 (t, 1H); 6.56 (dd, 1H); 6.42 (d, 1H); 6.35 (dd, 1H), 5.29 (d, 1H); 4.49 (d, 1H); 3.37 (d, 1H); 3.62 (bs, 2H); 1.86 (m, 3H), 1.7−1.3 (m., 12H).

(+)-*N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-(D-1,2-dihydroxypropylamino)phenyl)urea (63). To the solution of glyceraldehyde (0.02 g) and compound **62** (0.13 5 g, 0.24 mmol) in ethanol (3 mL) and dichloromethane (2 mL) at 23 °C, acetic acid (0.013 mL), sodium acetate trihydrate (0.040 g) and water (1 mL) were added. Sodium borohydride was then added portionwise during 30 min. and stirring continued for 3 h at 23 °C. After evaporation under vacuum the residue was treated with the same quantities of reagents under the same conditions. The reaction mixture was concentrated in vacuo, the residue taken up in dichloromethane (50 mL) and washed with water (20 mL) and brine (20 mL). The organic solution was dried, concentrated in vacuo and the residue was purified by flash chromatography on silica using CH/EA 1/1 and then methanol to give the title compound as a white solid (0.053 g, 0.08 mmol): TLC R_f = 0.64 (EA/MeOH, 7/3); $C_{36}H_{41}N_5O_5$; MS (FAB) *m/e* 624 (MH^+); IR ν_{max} 3377 (NH, OH), 1705 and 1659 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR δ 7.53 (bs, 1H); 7.46 (d, 1H); 7.42−7.2 (m, 7H); 7.14 (m, 1H); 6.97 (m, 2H); 6.74 (d, 1H); 6.64 (s 1H); 6.62 (d, 1H); 6.26 (d, 1H); 5.26 (d, 1H); 4.44 (d, 1H); 3.80 (m,1H); 3.64−3.44 (m, 2H); 3.35 (d, 1H); 3.20−2.98 (m, 2H); 1.86 (m, 3H); 1.7−1.3 (m, 12H).

***N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-(1,2-dihydroxypropylamino)phenyl)urea (64):** mp 267−8 °C; TLC R_f = 0.20 (CH/EA, 2:1); $C_{36}H_{41}N_5O_5$; IR ν_{max} 3302 (NH), 1713, 1674 and 1641 (C=O), 1612 and 1558 (C=C) cm^{-1}; ^1H NMR δ 7.52 (bt, 1H); 7.47 (d, 1H); 7.42−7.2 (m, 7H); 7.14 (t, 1H); 6.98 (d, 1H); 6.97 (m, 1H); 6.76 (m, 1H); 6.62 (m, 2H); 6.26 (d, 1H); 6.16 (d, 1H); 5.26 (d, 1H); 4.44 (d, 1H); 4.1 (bs,2H); 3.81 (m, 1H); 3.59 (bd, 1H); 3.49 (dd, 1H); 3.35 (d, 1H); 3.17 (d, 1H)), 1.86 (m, 3H); 1.7−1.3 (m, 12H).

***N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-acetamidophenyl)urea (65).** Acetyl chloride (0.011 g) was added to the racemic 3-amino derivative (0.07 g, 0.12 mmol) in MC (4 mL) and triethylamine (0.010 g). The mixture was stirred at 23 °C for 1 h, then filtered. The solid obtained was dissolved in MC (70 mL) and washed with water (30 mL), 20% sodium hydroxide solution (30 mL), 5% hydrochloric acid (30 mL) and water (30 mL), dried and concentrated in vacuo, to give the title compound as a gum (0.050 g, 0.08 mmol): TLC R_f = 0.82 (EA/MeOH, 9/1); $C_{35}H_{37}N_5O_4$; MS (FAB) *m/e* 592 (MH^+); IR ν_{max} 3346 (NH), 1701 and 1684 (C=O), 1607 and 1558 (C=C)cm^{-1}; ^1H NMR δ 9.83 (bs, 1H), 9.17 (bs, 1H); 7.83 (d, 1H); 7.64 (bs, 1H); 7.54 (t, 2H); 7.36 (t, 2H); 7.34 (m, 3H); 7.06 (m, 3H); 6.98−6.90 (m, 2H); 4.99 (d, 1H); 4.30 (d, 1H); 3.60 (d, 1H); 1.99 (s, 3H); 1.84 (bs, 3H); 1.70−1.2 (m, 12H).

***N*-[1-(Adamant-1-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-formilaminophenyl)urea (66).** To a solution of racemic 1-adamantan-

tylmethyl-2-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-aminophenyl)urea (0.175 g, 0.32 mmol) in formic acid (2 mL), acetic anhydride (0.7 mL) was added, and the reaction mixture was stirred at 15 °C for 3 h then at 20 °C for 20 h. The reaction mixture was concentrated in vacuo, taken up with MC (50 mL) and purified by flash chromatography, using CH/EA 1/1 as eluant to give a residue which was crystallized using MC/petroleum to give the title compound as a white solid (0.097 g, 0.16 mmol): TLC $R_f = 0.54$ (CH/EA, 1:9); MS (FAB) *m/e* 578 (MH^+); IR ν_{max} 3341 (NH), 1703 and 1645 (C=O), 1609 (C=C) cm^{-1}; ^1H NMR δ 8.58 (m, 1H); 8.10 (bs, 1H); 7.78 (bs, 1H); 7.76−7.69 (bs, 1H); 7.50−7.42 (m, 1H); 7.43−7.22 (m, 1H); 7.20−7.04 (m, 8H); 7.00−6.96 (dd, 1H); 6.88−6.60 (dd, 2H); 5.27 (d, 1H); 4.47 (m, 1H); 3.35 (m, 1H); 1.82−1.30 (m, 15H). Anal. ($C_{34}H_{35}N_5O_4$) H, N; C: calcd, 70.7; found, 67.86.

***N*-[1-(Bicyclo[2.2.1]hep-2-tyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(*N*,*N*-dimethylamino)phenyl]urea (71):** mp 258−9 °C; TLC $R_f = 0.62$ (CH/EA, 1:1); $C_{31}H_{33}N_5O_3$; MS (FAB) *m/e* 524 (MH^+); IR ν_{max} 3302 (NH), 1713, 1680 and 1637 (C=O), 1616 and 1558 (C=C) cm^{-1}; ^1H NMR δ 7.46−7.10 (m, 9H); 7.00 (m, 1H); 6.82 (dt, 1H); 6.58 (bd, 1H); 6.49 (bs, 1H); 6.46 (dd, 1H); 6.23 (bd, 1H); 5.29 (d, 1H); 4.45 (m, 1H); 3.47 and 2.65 (2bs, 1H); 3.93 and 3.92 (2s, 6H); 2.44 and 1.96 (2m, 1H); 2.25 and 2.17 (2bt, 1H); [[1.65−1.4 (m); 1.4−1.1 (m); 1.02 (m); 0.86 (m)] 7H].

***N*-[1-(Bicyclo[2.2.1]-2-hept-2-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-chlorophenyl)urea (72):** mp 193−4 °C; TLC $R_f = 0.62$ (CH/EA, 1:1); $C_{29}H_{27}ClN_4O_3$; MS (FAB) *m/e* 515 (MH^+); IR ν_{max} 3294 (NH), 1715, 1673 and 1649 (C=O), 1601 and 1551 (C=C) cm^{-1}; ^1H NMR δ [[7.64−7.14 (m,); 7.06−6.98 (m); 6.98−6.84 (m), 14H]; 6.64 (2d, 1H); 5.29 (2d, 1H); 4.45 (m, 1H); 3.45 and 2.63 (2s, 1H); 2.35 (m, 1H); 2.16 (m, 1H); 1.97 (m, 1H); 1.65−0.87 (m, 7H).

***N*-[1-(Adamant-2-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(*N*,*N*-dimethylamino)phenyl]urea (73):** mp 229−30 °C; TLC $R_f = 0.55$ (CH/EA, 1:1); $C_{35}H_{39}N_5O_3$; MS (FAB) *m/e* 578 (MH^+); IRν_{max} 3310 (NH), 1715 and 1668 (C=O), 1641 and 1614 (C=C) cm^{-1}; ^1H NMR δ 7.5−7.11 (m, 9H); 6.98 (m, 1H); 6.83 (t, 1H); 6.58 (m, 1H); 6.46 (m, 1H); 6.50 (m, 1H); 6.31 (d, 1H); 5.29 (d, 1H); 5.05 (m, 1H); 3.58 (m, 1H); 2.92 (s, 6H); 2.04 (m, 1H); 1.9−1.4 (m, 14H).

General Procedure To Obtain Compounds of General Formula I via Carbamate 10 (Scheme 3). *N*-[2,4-Dioxo-5-(2-fluorophenyl)-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-(*N*,*N*-dimethylamino)-phenyl)urea (30). Triethylamine (0.32 mL, 2.31 mmol) and 3-*N*,*N*-dimethylaminoaniline dihydrochloride (0.24 g, 1.15 mmol) were added to a suspension of the intermediate **10c** (0.22 g, 0.46 mmol) in dry dimethylformamide (5 mL) under a nitrogen atmosphere. The resulting mixture was heated at 160 °C for 2 h, then cooled to room temperature, diluted with water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried, concentrated in vacuo and the residue was triturated with acetonitrile to give the title compound as a white solid (0.12 g, 50%): mp 252−3 °C; TLC $R_f = 0.50$ (CH/EA 1:1); $C_{29}H_{32}FN_5O_3$. Analytical data in agreement with those obtained following method iii.

Analytical data for representative compounds are as follows.

***N*-[1-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-*N*,*N*-dimethylaminophenyl)urea (34):** TLC $R_f = 0.31$ (CH/EA, 1:1); mp 221−3 °C; $C_{30}H_{35}N_5O_3$; MS (FAB) *m/e* 514; IR ν_{max} 3500 (NH), 1794, 1707 and 1666 (C=O); 1607 (C=C) cm^{-1}; ^1H NMR δ 7.46−7.10 (m, 9H); 6.99 (dd, 1H); 6.82 (t, 1H); 6.60 (m, 1H); 6.46 (m, 1H); 6.53 (bs, 1H); 6.31 (d, 1H); 5.31 (d, 1H); 4.47 (m, 1H); 3.69 (m, 1H); 2.94 (s, 3H); 2.93 (s, 3H); 1.47 (m, 2H); 0.94 (s, 9H).

***N*-[1-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-methylthiophenyl)urea (35):** TLC $R_f = 0.62$ (CH/EA, 1:1); mp 247−9 °C; $C_{29}H_{32}N_4O_3S$; MS (CI) *m/e* 517; IR ν_{max} 3300 (NH), 1705, 1674 and 1641 (C=O); 1607 (C=C) cm^{-1}; ^1H NMR δ 7.48−7.10 (m, 10H);7.02−6.90 (m, 3H); 6.82 (s, 1H); 6.30 (d, 1H); 5.30 (d, 1H); 4.46 (m, 1H); 3.70 (m, 1H); 2.44 (s, 3H); 1.48 (t, 2H); 0.93 (s, 9H).

***N*-[1-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-dimethylamino)phenylurea (41):** mp 255−6 °C; TLC $R_f = 0.28$ (CH/EA); $C_{30}H_{34}FN_5O_3$; MS (FAB) *m/e* 530 (MH^+); IR ν_{max} 3308 (NH), 1717 (C=O), 1637 (C=C) cm^{-1}; ^1H NMR δ 7.48−7.10 (m, 8H); 6.98 (dd, 1H); 6.81 (t, 1H); 6.66−6.56 (m, 2H); 6.46 (dd, 1H); 6.34 (d, 1H); 5.36 (d, 1H); 4.41 (m, 1H); 3.70 (m, 1H); 2.94 (s, 3H); 2.92 (s, 3H); 1.49 (t, 2H); 0.93 (s, 9H).

***N*-[1-(Adamant-1-ylethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-*N*,*N*-dimethylaminophenyl)urea (67):** TLC $R_f = 0.37$ (CH/EA 1:1); $C_{36}H_{41}N_5O_3$; MS (FAB) *m/e* 592; IR ν_{max} 3373 (NH), 1707, 1682 and 1660 (C=O); 1595 and 1580 (C=C) cm^{-1}; ^1H NMR δ 7.45−6.35 (m, 3H); 7.34−7.26 (m, 2H); 7.22−7.15 (m, 3H); 7.12 (t, 1H); 6.98 (dd, 1H); 6.84 (t, 1H); 6.74 (bs, 1H); 6.56 (dd, 1H); 6.44 (dd, 1H); 6.42 (d, 1H); 5.31 (d, 1H); 4.52−4.42 (m, 1H); 3.72−3.62 (m, 1H); 2.91 (s, 6H); 1.94 (bs, 3H); 1.67 (bq, 6H); 1.50 (d, 6H); 1.33 (t, 2H).

***N*-[1-(Adamant-1-ylethyl)-2,4-dioxo-5-phenyl -2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-methylthiophenyl)-urea (68):** TLC $R_f = 0.75$ (CH/EA, 1:1); MS (FAB) *m/e* 595 (MH^+); $C_{35}H_{38}N_4O_3S$; IR ν_{max} 3430 (NH), 1701 and 1670 (C=O); 1595 (C=C) cm^{-1}; ^1H NMR δ 7.5−6.88 (m, 13H); 6.42 (d, 1H); 5.31 (d, 1H); 4.48 (m, 1H); 3.70 (m, 1H); 2.43 (s, 3H); 2.09−1.3 (m, 18H).

***N*-[1-(Adamant-2-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(*N*,*N*-dimethylamino)phenyl]urea (69):** TLC $R_f = 0.72$ (MC/MeOH, 95:0.5); $C_{34}H_{37}N_5O_3$; IR ν_{max} 3300 (NH), 1713 and 1676 (C=O), 1637 and 1610 (C=C) cm^{-1}; ^1H NMR δ 7.4−7.1 (m, 9H); 6.99 (m, 1H); 6.80 (t, 1H); 6.62 (m, 1H); 6.56 (dd, 1H); 6.45 (dd, 1H); 6.31 (d, 1H); 5.31 (d, 1H); 4.52 (m, 1H); 2.91 (m, 7H); 2.32 (m, 1H); 2.0−1.1 (m, 12H).

General Procedure To Obtain Compounds of General Formula I via Isocianato 9 (Scheme 3). *N*-[1-(3-Cyclopentylprop-2-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(tetrazol-5-yl)phenyl]-urea (42). Phosgene in toluene (1.93 M solution, 5 mL) was added to a solution of the intermediate **5h** (0.130 g, 0.34 mmol) in dry dichloromethane (10 mL). The resulting solution was stirred at 23 °C for 7 h, then concentrated in vacuo at 50 °C for 3 h to give the 1-(3-cyclopentylprop-2-yl)-2,4-dioxo-3-isocyanato-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine as crude. 5-(3-Aminophenyl)tetrazole (0.40 mg) was added to a solution of the above intermediate in acetonitrile (8 mL) under nitrogen atmosphere and stirring was continued for 7 h, then concentrated in vacuo and purified by flash chromatography (eluting with MC increasing polarity to MC methanol (9:1) to give the title compound (0.025 g, 0.04 mmol) as a white solid: TLC $R_f = 0.43$ (MC/MeOH, 9:1); C_{31} H_{32} N_8O_3; MS (FAB) *m/e* 565 (MH^+); IR ν_{max} 3335 (NH), 1693 and 1647 (C=O, C=N) cm^{-1}; ^1H NMR δ 8.82−8.66 (m, 1H); 7.48 (m, 3H); 7.42−6.80 (m, 13H); 5.29 (m, 1H); 4.53 (m, 1H); 2.20−1.20 (m, 9H); 1.16−0.80 (m, 2H); 1.36 (d, 3H).

***N*-[2,4-Dioxo-5-(2-fluorophenyl)-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-methylthiophenyl)urea (33):** mp 246−7 °C; TLC $R_f = 0.65$ (CH/EA,1:1); $C_{27}H_{27}FN_4O_3$; MS (FAB) *m/e* 475 (MH^+); IR ν_{max} 1711, 1691, 1680 and 1670 (C=O), 1595 (C=C) cm^{-1}; ^1H NMR δ 7.46 (dd, 1H); 7.4−7.30 (m, 3H); 7.26−7.10 (m, 4H); 7.04−6.9 (m, 3H); 6.82−6.76 (bm, 1H); 6.26 (d, 1H); 5.33 (d, 1H); 4.46 (m, 1H); 3.70 (m, 1H); 2.44 (s, 3H); 1.6−1.4 (m, 3H); 0.91 (d, 3H); 0.89 (d, 3H).

***N*-[1-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-cyanophenyl)-urea (36):** mp 268−70 °C; TLC $R_f = 0.55$ (CH/EA, 1:1); $C_{29}H_{29}N_5O_3$; IR ν_{max} 3319 (NH), 2230 (C=N), 1711 and 1647 (C=O) cm^{-1}; ^1H NMR δ 7.91 (bs, 1H); 7.52−7.12 (m, 12H); 7.01 (dd, 1H); 6.88 (d, 1H); 5.34 (d, 1H); 4.52−4.38 (m, 1H); 3.80−3.68 (m, 1H); 1.51 (m, 2H); 0.91 (s, 9H).

***N*-[1-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(tetrazol-5-yl)phenyl]urea (37):** TLC $R_f = 0.44$ (MC/MeOH, 80:20); MS (CI) *m/e* 538 (MH^+); $C_{29}H_{30}N_8O_3$+10% mol TEA; IR ν_{max} 3310 (NH), 1691, 1657 and 1641 (C=O) cm^{-1}; ^1H NMR δ 9.46 (s, 1H); 8.16 (bs, 1H); 7.78 (dd, 1H); 7.58 (dt, 1H); 7.52−7.28 (m, 8H); 7.21 (d, 2H); 7.01 (m, 2H); 5.04 (d, 1H); 4.38 (m, 1H); 3.83 (m, 1H); 1.40 (t, 2H); 0.92 (s, 9H).

***N*-[1-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-[2-(2,2-dimethylethyl)tetrazol-5-yl]phenyl]urea (38):** mp 266−8 °C; TLC $R_f = 0.13$ (CH/EA, 7:3); MS (FAB) *m/*e (MH^+) 595; $C_{33}H_{38}N_8O_3$; IR ν_{max} 3320 (NH), 1715, 1668 and 1645 (C=O), 1599 (C=C) cm^{-1}; ^1H NMR δ 8.03 (t, 1H); 7.81 (dt, 1H); 7.46 (dd, 1H); 7.44−7.15 (m, 10H); 7.00 (dd, 1H); 6.48 (d, 1H); 5.36 (d, 1H); 4.54−4.42 (m, 1H); 3.78−3.64 (m, 1H); 1.77 (s, 9H); 1.54−1.44 (m, 2H); 0.91 (s, 9H).

***N*-[1-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(3-trifluoromethoxyphenyl)urea (39):** mp 234−5 °C; TLC $R_f = 0.57$ (CH/EA, 60:40); MS (CI) *m/e* 555 (MH^+); $C_{29}H_{29}F_3N_4O_4$; IR ν_{max} 3317 (NH), 1717 and 1650 (C=O); 1609 and 1558 (C=C) cm^{-1}; ^1H NMR δ 7.53 (bs, 1H); 7.46 (dd, 1H); 7.45−7.18 (m, 8H); 7.10 (t, 1H); 7.00 (dd, 1H); 6.88 (m, 1H); 6.77 (m, 1H); 6.66 (d, 1H); 5.35 (d, 1H); 4.45 (m, 1H); 3.70 (m, 1H); 1.54−1.42 (m, 2H); 0.91 (s, 9H).

***N*-[1-(3,3-Dimethylbut-1-yl)-2,4-dioxo-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-(methylthiophenyl)urea (40):** mp 249−50 °C; TLC $R_f = 0.33$ (CH/EA, 7:3); $C_{29}H_{31}FN_4O_3S$; MS (FAB) *m/e* 536 (MH^+); IR ν_{max} 3308 (NH), 1707, 1676 and 1643 (C=O), 1607 (C=C) cm^{-1}; ^1H NMR δ 7.48−6.90 (m, 12H); 6.83 (bs, 1H); 6.29 (d, 1H); 5.34 (d, 1H); 4.41 (m, 1H); 3.71 (m, 1H); 2.44 (s, 3H); 1.50 (m, 2H); 0.93 (s, 9H).

***N*-[1-(2-Cyclopentylethyl)-2,4-dioxo-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(dimethylamino)phenyl]urea (43):** mp 238−40 °C; TLC R_f = 0.90 (MC/MeOH, 9:1); $C_{31}H_{34}FN_5O_3$; MS (FAB) *m/e* 544 (MH^+); IR ν_{max} 3400 (NH), 1707, 1676 and 1637 (C=O and C=N), 1600 (C=C) cm^{-1}; ^1H NMR δ 7.46 (dd, 1H); 7.42−7.10 (m, 6H); 7.14 (t, 1H); 6.98 (dd, 1H); 6.82 (t, 1H); 6.61 (dd, 1H); 6.56 (bs, 1H); 6.46 (dd, 1H); 6.33 (d, 1H); 5.36 (d, 1H); 4.49−4.39 (m, 1H); 3.74−3.64 (m, 1H); 2.92 (s, 6H); 1.66−1.54 (bm, 3H); 1.66−1.40 (bm, 6H); 1.16−1.04 (bm, 2H).

***N*-[1-(2-Cyclopentylethyl)-2,4-dioxo-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[4-(dimethylamino)phenyl]urea (44):** TLC R_f = 0.81 (MC/MeOH, 9:1); $C_{31}H_{34}FN_5O_3$; MS (FAB) *m/e* 544 (MH^+); IR ν_{max} 3304 (NH), 1718−1641 (C=O), 1605−1549 (C=C) cm^{-1}; ^1H NMR δ 7.46 (dd, 1H); 7.40−7.10 (m, 8H); 6.98 (dd, 1H); 6.68 (d, 2H); 6.28 (bs, 1H); 6.07 (d 1H); 5.32 (d, 1H); 4.41 (m,1H); 3.66 (m, 1H); 2.91 (s, 6H); 1.84−1.00 (m, 11H).

***N*-[1-(2-Cyclopentylethyl)-2,4-dioxo-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(methylthio)phenyl]urea (45):** mp 220−3 °C; TLC R_f = 0.69 (EA/CH, 1:1); $C_{30}H_{31}FN_4O_3S$; MS (FAB) *m/e* 547 (MH^+); IR ν_{max} 3300 (NH), 1703, 1674 and 1639 (C=O), 1607 (C=C) cm^{-1}; ^1H NMR δ 9.23 (s, 1H); 7.78 (d, 1H); 7.54−7.38 (m, 7H); 7.04−6.94 (m, 3H); 7.16 (t, 1H); 6.80 (m, 1H); 5.07 (d, 1H); 4.42−4.32 (m, 1H); 3.86−3.77 (m, 1H); 2.41 (s, 2H); 1.80−1.6 (m, 3H); 1.6−1.36 (m, 6H); 1.14−1.00 (m, 2H).

***N*-[1-(2-Cyclopentylethyl)-2,4-dioxo-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(5-tetrazol-5-yl)phenyl]urea (46):** TLC R_f = 0.55 (MC/MeOH, 8:2); $C_{30}H_{29}FN_8O_3$; MS (FAB) *m/e* 569 (MH^+); IR ν_{max} 3330−3200 (NH), 1697, 1664 and 1637 (C=O and C=N), 1595 (C=C) cm^{-1}; ^1H NMR δ 9.46 (bs, 1H); 8.19 (bs, 1H); 7.79 (dd, 1H); 7.62−7.28 (m, 10H); 7.06 (d, 1H); 7.02 (dd, 1H); 5.10 (d, 1H); 4.38 (m, 1H); 3.81 (m, 1H); 1.82−1.62 (m, 3H); 1.60−1.36 (m, 6H); 1.16−1.00 (m, 2H).

***N*-[1-(Adamant-2-yl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl]-*N*′-[3-(tetrazol-5-yl)phenyl]urea (70):** TLC R_f = 0.58 (MC/MeOH, 8:2); $C_{33}H_{32}N_8O_3$; MS (FAB) *m/e* 589 (MH^+); IR ν_{max} 3325 (NH), 1684 (C=O), 1661 (C=O and C=N), 1593 (C=C) cm^{-1}; ^1H NMR δ 9.26 (s, 1H); 7.99 (m, 1H); 7.67 (m, 1H); 7.56−7.46 (m, 3H); 7.42−7.32 (m, 5H); 7.28 (m, 1H); 7.24 (d, 1H); 6.98 (m, 1H); 6.89 (d, 1H); 5.05 (d,1H); 4.53 (m, 1H); 2.91 (m, 1H); 2.30 (m, 1H); 1.94−1.04 (m, 12H).

General Procedure for Resolution. 1-(Adamant-1-ylmethyl)-3-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (1*S*)-(+)-10-Camphorsulfonate (74m). A solution of (1*R*)-(−)-10-camphorsulfonic acid (0.347 g, 1.49 mmol) in ethyl acetate (11 mL) was added to a hot solution of the racemic amine **5m** (0.74 g, 1.78 mmol) in ethyl acetate (1 mL). The resulting precipitate was filtered, washed with cold ethyl acetate to give a (+):(−) 60:40 mixture of diastereomeric salts (0.836 g, 1.29 mmol). Recrystallization from chloroform-methanol (50:50, 6 mL) gave a (+):(−) 88:12 mixture of diastereomeric salts (0.195 g, 0.30 mmol) as white crystals. The mother liquors were concentrated in vacuo to give an enriched mixture of diastereomeric salt (0.93 g, 1.43 mmol). A solution of this material in dichloromethane (40 mL) was washed with a 5% ammonia solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried and concentrated in vacuo to give an enriched mixture of amines (0.55 g). To a hot solution of this material in chloroform (25 mL) (1*S*)-(+)-10-camphorsulfonic acid (0.277 g, 1.19 mmol) was added; the mixture was concentrated to a small volume (5 mL), then methanol was added dropwise (5 mL). The resulting solid was filtered off and washed with cold methanol to give the title compound (0.34 g, 0.52 mmol) as white needles: $[\alpha]_D = -18.4$ (CH_2Cl_2 $c = 0.7565$); $C_{36}H_{45}N_3O_6S$; MS (FAB) *m/e* 416 (MH^+); IR ν_{max} 1734, 1714 and 1684 (C=O) cm^{-1}; ^1H NMR δ 7.52 (dd, 1H); 7.44- -7.24 (m, 6H); 7.18 (dt, 1H); 7.00 (dd, 1H); 4.93 (s, 1H); 4.49(d, 1H); 3.44 (d, 1H); 3.19 (d, 1H); 2.75 (d, 1H); 2.46−1.20 (m, 20H); 0.99 (s, 3H); 0.78 (s, 3H).

1-(Adamant-1-ylmethyl)-3-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (1*R*)-(−)-10-Camphorsulfonate (75m). The mother liquors recovered after the crystallization of the above intermediate **74m** were concentrated in vacuo to give an enriched mixture of diastereomeric salt (0.421 g, 0.64 mmol). A solution of this material in dichloromethane (40 mL) was washed with a 5% ammonia solution (2 × 25 mL) and brine (2 × 20 mL). The organic layer was dried and concentrated in vacuo to give an enriched mixture of amines (0.256 g, 0.61 mmol). To a hot solution of this material in chloroform (10 mL) (1*R*)-(−)-10-camphorsulfonic acid (0.13 g, 0.55 mmol) was added; the mixture was concentrated to a small volume (3 mL), then methanol was added dropwise (3 mL). The resulting solid was filtered off and washed with cold methanol to give the title compound as white needles (0.216 g, 0.33 mmol): $[\alpha]_D = +21.27$ (CH_2Cl_2 c = 0.6500); $C_{36}H_{45}N_3O_6S$; MS (FAB) *m/e* 416 (MH^+); IR ν_{max} 1734, 1711 and 1684 (C=O) cm^{-1}; ^1H NMR δ 7.52 (dd, 1H); 7.44−7.24 (m, 7H); 7.19 (m, 1H); 7.01 (dd, 1H); 5.00 (s, 1H); 4.48 (d, 1H); 3.45 (d, 1H); 3.18 (d, 1H); 2.75 (d, 1H); 2.40−2.22 (m, 2H); 2.04−1.24 (m, 20H); 0.99 (s, 3H); 0.78 (s, 3H).

3-Amino-2,4-dioxo-1-(3-methylbut-1-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (1*S*)-(+)-10-Camphorsulfonic Salt (74b). To the racemic amine **5b** (2.05 g, 6.07 mmol) dissolved in hot ethyl acetate (35 mL), (1*S*)-(+)-10-camphorsulfonic acid (0.95 g, 4.08 mmol) was added. The resulting salt was crystallized out from the cooled solution by dropwise addition of cyclohexane; the precipitate was filtered off and washed with cold cyclohexane to give a (+)/(−) 3/97 mixture of diastereomeric salt (1.1 g, 1.94 mmol). Recrystallization from 2-propanol afforded the pure title compound (0.49 g, 0.86 mmol): $[\alpha]_D = -68.11$ (CH_2Cl_2 $c = 1.0055$). Recrystallization from methanol gave the title compound (0.34 g, 0.52 mmol) as white needles: $[\alpha]_D = -18.4$ (CH_2Cl_2 $c = 0.7565$); $C_{30}H_{39}N_3O_6S$; MS (FAB) *m/e* 570 (MH^+); IR ν_{max} 2750−2600 (NH_3), 1736,1713 and 1700 (C=O) cm^{-1}; ^1H NMR δ 9.0−7.4 (bm, 2H); 7.5 (d, 1H): 7.45−7.2 (m, 6H); 7.18 (t, 1H); 6.97 (d, 1H); 5.05 (s, 1H); 4.58 (m, 1H); 3.68 (m, 1H); 3.20 (m, 2H); 2.72 (m, 1H); 2.42 (m, 1H); 2.22 (m, 1H); 2.0 (m, 6H); 1.2 (m, 2H); 1.0−0.7 (m, 12H).

3-Amino-2,4-dioxo-1-(3-methylbut-1-yl)-5-phenyl-2,3,4,5-

tetrahydro-1*H*-1,5-benzodiazepine (1*R*)-(−)-10-Camphorsulfonic Salt (75b). The mother liquors obtained after precipitation of the above compound **74b** were evaporated to dryness to give an enriched mixture of diastereomeric salt (2.19 g,). The residue was taken up in ethyl acetate (30 mL), extracted with a 5% ammonia solution (20 mL) and washed with brine (20 mL). The organic layer was dried and evaporated in vacuo, to give the enriched mixture of amine (1.0 g, 2.96 mmol). (1*R*)-(−)-10-Camphorsulfonic acid (0.47 g, 2.04 mmol) in ethyl acetate (6 mL) was added to the solution of the above amine (1 g) in ethyl acetate (5 mL) and the resulting solution was stirred at 0 °C for 2 h. The obtained precipitate was filtered off, washed with EA (20 mL) and dried to give the title compound (0.97 g, 1.70 mmol): $[\alpha]_D = +71$ (CH_2Cl_2 c = 0.606). Recrystallization from methanol gave the title compound (0.34 g, 0.52 mmol) as white needles: $[\alpha]_D = -18.4$ (CH_2Cl_2 c = 0.7565); $C_{20}H_{23}N_3O_2 \cdot C_{10}H_{16}O_4S$; MS (FAB) *m/e* 569 ($MH^+$); ^{1}H NMR δ 9.0−7.4 (bm, 2H); 7.5 (d, 1H): 7.45−7.2 (m, 6H); 7.18 (t, 1H); 6.97 (d, 1H); 5.05 (s, 1H); 4.58 (m, 1H); 3.68 (m, 1H); 3.20 (m, 2H); 2.72 (m, 1H); 2.42 (m, 1H); 2.22 (m, 1H); 2.0 (m, 6H);1.2 (m, 2H); 1.0−0.7 (m, 12H).

3-Amino-2,4-dioxo-5-(2-fluorophenyl)-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (1*R*)-(−)-10-Camphorsulfonate (74c). A hot solution of (1*R*)-(−)-10-camphorsulfonic acid (1.685 g, 7.26 mmol) in ethyl acetate (15 mL) was added, dropwise over 30 min, to a solution of the amine **5c** (3.0 g, 8.44 mmol) in ethyl acetate (7 mL) previously heated at 90 °C under a nitrogen atmosphere. The resulting solution was heated at 90 °C for 10 min, then concentrated in vacuo. The residue was triturated with EE−petroleum gave a (+)/(−) 50/50 mixture of diastereomeric salt (4.65 g). Recrystallization from 2-propanol gave the title compound (0.9 g, 1.5 3 mmol): $[\alpha]_D = +67.8$ (CH_2Cl_2 c = 0.52); mp 216−7 °C; $C_{20}H_{22}FN_3O_2 \cdot C_{10}H_{16}O_4S$; MS (FAB) *m/e* 588 ($MH^+$); IR (Nujol) ν_{max} 1736, 1717 and 1700 (C=O) cm^{-1}; ^{1}H NMR δ 7.8−7.7 (bs, 3H); 7.47 (d, 1H); 7.4−7.03 (m, 6H); 7.00 (dd., 1H); 5.08 (s, 1H); 4.47 (m, 1H); 3.69 (m, 1H); 3.19 (d, 1H); 2.71 (d, 1H); 2.4 (m, 1H); 2.24 (d, 1H); 2.00−1.36 (m, 8H); 0.97 (s, 3H); 0.89 (d, 3H); 0.87 (d, 3H); 0.76 (s, 3H).

3-Amino-2,4-dioxo-5-(2-fluorophenyl)-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (1*S*)-(+)-10-Camphorsulfonate (75c). The mother liquors obtained after precipitation of the above intermediate **74c** were concentrated in vacuo to dryness to give an enriched mixture of diastereomeric salt (3.7 g, 6.3 mmol). A solution of this material in ethyl acetate (100 mL) was washed with a 5% ammonia solution (2 × 60 mL) and brine (100 mL). The organic layer was dried and evaporated in vacuo to give the enriched mixture of amine (1.88 g, 84%). A hot solution of (1*S*)-(+)-10-camphorsulfonic acid (1.01 g, 4.35 mmol) in ethyl acetate (9 mL) was added dropwise over 15min to a solution of the above mixture (1.8 g, 5 mmol) in ethyl acetate (4 mL) previously heated at 90 °C under a nitrogen atmosphere. The resulting solution was heated to 90 °C for 10 min, then concentrated in vacuo. The residue was triturated with EE−petroleum to give a (+)/(−) 55/45 mixture of diastereomeric salt (2.8 g). Recrystallization from 2-propanol gave the title compound (0.5 g, 1.00 mmol): mp 216−7 °C; $[\alpha]_D = -73.1$ (CH_2Cl_2 c = 0.59); MS (FAB) *m/e* 588 (MH^+); IR (Nujol) ν_{max} 1736, 1717 and 1688 (C=O) cm^{-1}; ^{1}H NMR δ 7.8 (m, 2H); 7.5 (d, 1H); 7.4−7.1 (m, 7H); 7.00 (d, 1H); 5.09(s, 1H); 4.49 (m, 1H); 3.70 (m, 1H); 3.20 (d, 1H); 2.72 (d, 1H); 2.40 (m, 1H); 2.25 (m, 1H); 2.00−1.3 (m, 8H); 0.98 (s, 3H); 0.90 (d, 3H); 0.88 (d, 3H); 0.77 (s, 3H).

(−)-1-(Adamant-1-ylmethyl)-3-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (76m). A solution of the intermediate **74m (**0.311 g, 0.74 mmol) in chloroform (40 mL) was washed with a 5% ammonia solution (3 × 25 mL) and brine (3 × 20 mL). The organic layer was dried and concentrated in vacuo to give the title compound as a white foam (0.19 g, 0.45 mmol, 95%): 95%; TLC R_f 0.33 (EA/MeOH 95:5); $[\alpha]_D = -36.8$ (CH_2Cl_2 c = 0.4945); MS (FAB) *m/e* 416 (MH^+); IR ν_{max} 3369 (NH_2), 1701−1672 (C=O), cm^{-1}; ^{1}H NMR δ 7.47 (dd, 1H); 7.40−7.30 (m, 5H); 7.23 (td, 1H); 7.15 (td, 1H); 6.94 (dd, 1H); 4.52 (d, 1H); 3.38 (d, 1H); 4.22 (s, 1H); 2.30−1.70 (m, 2H); 1.82 (m, 3H); 1.70−1.30 (m, 12H).

(+)-1-(Adamant-1-ylmethyl)-3-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (77m): TLC R_f = 0.33 (EA/MeOH 95:5); $[\alpha]_D = +31$ (CH_2Cl_2 c = 0.496); MS (FAB) *m/e* 416 (MH^+); IR ν_{max} 3369 (NH_2), 1701−1672 (C=O) cm^{-1}; ^{1}H NMR δ 7.5 (dd, 1H); 7.40−7.30 (m, 5H); 7.23 (td, 1H); 7.15 (td, 1H); 6.94 (dd, 1H); 4.52 (d, 1H); 3.38 (d, 1H); 4.22 (s, 1H); 2.30−1.70 (m, 2H); 1.82 (m, 3H); 1.70−1.30 (m, 12H).

(−)-3-Amino-2,4-dioxo-1-(3-methylbut-1-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (76b): TLC R_f = 0.55 (MC/methanol, 95:5); $[\alpha]_D = -114$ (CH_2Cl_2 c = 0.5805); MS (FAB) *m/e* 338 (MH^+); IR ν_{max} 3377 (NH_2), 1705−1670 (C=O), 1593 (C−C) cm^{-1}; ^{1}H NMR δ 7.5−7.1 (m, 8H); 6.95 (dd, 1H); 4.55 (m, 1H); 4.23 (s, 1H); 3.7 (m, 1H); 1.8 (m, 2H); 1.64−1.4 (m, 3H); 0.92 (d, 3H); 0.89 (d, 3H).

(+)-3-Amino-2,4-dioxo-1-(3-methylbut-1-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (77b): $[\alpha]_D = +107.5$ (CH_2Cl_2 c = 5.355 mg/mL); IR ν_{max} 3375 (NH_2), 1715−1661 (C=O), 1591 (C−C) cm^{-1}; ^{1}H NMR δ 7.5−7.1 (m, 8H); 6.95 (dd, 1H); 4.6−4.5 (m, 1H); 4.24 (s, 1H); 3.8−3.65 (m, 1H); 1.8 (bs, 2H); 1.62−1.4 (m, 3H); 0.92 (d, 3H); 0.89 (d, 3H).

3-(−)-Amino-2,4-dioxo-5-(2-fluorophenyl)-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (76c): 96%; mp 125−6 °C; TLC R_f = 0.38 (MC/MeOH, 30:1); $[\alpha]_D = -117.4$ (CH_2Cl_2 c = 2.9 mg/mL); MS (FAB) *m/e* 356 (MH^+); IR (Nujol) ν_{max} 1717 and 1701 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR δ 7.42 (dd, 1H); 7.40−7.18 (m, 6H); 6.94 (dd, 1H); 4.54 (m, 1H); 4.28 (s, 1H); 3.70 (m, 1H); 2.8−1.6 (m, 2H); 1.78−1.4 (m, 3H); 0.92 (d, 3H); 0.90 (d, 3H).

3-(+)-Amino-2,4-dioxo-5-(2-fluorophenyl)-1-(3-methylbut-1-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (77c): 97%; mp 125−6 °C; TLC R_f = 0.38 (MC/MeOH, 30:1); $[\alpha]_D = +115.2$ (CH_2Cl_2 c = 2.75 mg/mL); MS (FAB) *m/e* 356 (MH^+); IR (Nujol) ν_{max} 3375 and 3317 (NH), 1699 and 1666 (C=O), 1591 (C=C) cm^{-1}; ^{1}H NMR δ 7.42 (dd, 1H); 7.40−7.18 (m, 6H); 6.94 (dd, 1H); 4.54 (m, 1H); 4.28 (s, 1H); 3.70 (m, 1H); 2.8−1.6 (m, 2H); 1.78−1.4 (m, 3H); 0.92 (d, 3H); 0.90 (d, 3H).

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Supporting Information Available: Crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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