Novel, Achiral 1,3,4-Benzotriazepine Analogues of 1,4-Benzodiazepine-Based CCK_2 Antagonists That Display High Selectivity over CCK_1 Receptors

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A series of 1,3,4-benzotriazepine-based CCK_2 antagonists have been devised by consideration of the structural features that govern CCK receptor affinity and the receptor subtype selectivity of 1,4-benzodiazepine-based CCK_2 antagonists. In contrast to the latter compounds, these novel 1,3,4-benzotriazepines are achiral, yet they display similar affinity for CCK_2 receptors to the earlier molecules and are highly selective over CCK_1 receptors.

Introduction

One approach to blocking the actions of the peptide hormone gastrin has been through the use of CCK_2 (formerly CCK_B, CCK_B/gastrin, or CCK_2/gastrin) receptor antagonists.[1] Due to the role of gastrin in the stimulation of gastric acid secretion and in gastrointestinal cell growth, such compounds have been considered likely to be beneficial in the treatment of some gastric acid related disorders, such as gastro esophageal reflux disease (GERD) and proton pump inhibitor (PPI)-evoked rebound acid hypersecretion, as well as in certain GI tumors.[2,3] In addition, the location of CCK_2 receptors in the central nervous system (CNS) and the association of their activation by the related hormone cholecystokinin (CCK), with the mediation of pain, panic, and anxiety, have raised the possibility that CCK_2 antagonists may also have a role in controlling these disorders.[4,5] However, a key consideration in devising antagonists of CCK_2 receptors, whether in the periphery or in the CNS, is that they should be selective for these receptors over the related CCK_1 (formerly CCK_A) receptor. In contrast to CCK_2 receptors, which can be activated by gastrin or CCK, CCK_1 receptors are only activated to full effect by CCK. In the periphery, CCK_1 receptors are involved in gallbladder contraction and pancreatic secretion, and in the CNS, they are associated with food intake.[6] CCK receptors are archetypal class A, 7-transmembrane G-protein coupled receptors, and the availability of selective ligands for the receptor subtypes has helped to bring a clearer understanding of the pharmacology associated with their activation by gastrin and/or CCK.

CCK_2 receptor antagonists span a diverse range of chemical structures that have been devised by one of two main approaches.[7] The peptoid-based compound CI-988[8] and the indole derivative JB93182[9] are the most significant examples to stem from using the native peptide hormone as the starting point. Neither of these ligands represents a viable drug candidate, partly due to their low oral potency. However, the discovery by workers at Merck that the natural product asperlicin exhibited weak activity at CCK_1 receptors prompted much effort in deriving CCK antagonists by using it as the starting point. By focusing on the 1,4-benzodiazepine (BDZ) ring system that comprised part of the structure of asperlicin, they devised potent and selective antagonists for both CCK receptor subtypes in which ligand stereochemistry influenced receptor affinity and subtype selectivity (Chart 1). In particular (3*S*)-**1** (L-364,718),[10,11] which has a 3-amino-(1*H*-indol-2-oyl) substituent was considered optimum for high CCK_1 affinity and selectivity (Table 1).[11] Although the enantiomer, (3*R*)-**1**, shared the same receptor subtype preference, it was less potent than (3*S*)-**1** at CCK_1 receptors. This receptor selectivity profile was maintained when the substituent attached to the C-3 position was changed from amino-(1*H*-indol-2-oyl) to *N*,*N*′-(*m*-tolyl)-urea but only in the case of the 3*S* enantiomer ((3*S*)-**2**), since the corresponding enantiomer ((3*R*)-**2**, L-365,260)[12] displayed high affinity and selectivity for CCK_2 receptors.[13] Compound (3*R*)-**2** represents a milestone in CCK_2 antagonist research and has prompted efforts to obtain superior compounds based on a 1,4-BDZ framework. However, this approach has been influenced by the divergent biological profiles observed for the separate stereoisomers of the same compound, such as (3*S*)-**2** and (3*R*)-**2**, and ligand stereochemistry has played a central role in obtaining novel compounds of this type with high affinity for CCK_2 receptors and selectivity over CCK_1 receptors.

Compound (3*R*)-**3** (YF476) was one of the most potent 1,4-BDZ-based CCK_2 selective antagonists that followed from this approach.[14] The (3*R*)-**3** had the same configuration as (3*R*)-**2**, but in contrast to the latter compound, where inversion of configuration afforded the CCK_1 selective compound (3*S*)-**2**, the equivalent change to (3*R*)-**3** yielded a molecule, (3*S*)-**3**, that maintained selectivity for CCK_2 receptors.[15] Thus (3*S*)-**3** benefited from both enhanced CCK_2 receptor interaction and reduced affinity for CCK_1 receptors compared to an N-1 methyl-substituted derivative such as (3*S*)-**2**. This trend in behavior is also evident from consideration of the biological profiles of other 1,4-BDZ-based CCK ligands containing bulky N-1 substituents,[16,17] indicating that in contrast to the N-1 methyl substituted 1,4-BDZ-based CCK_2 antagonists,[13,17,18] CCK receptor subtype selectivity is independent of configuration at C-3. 1,5-BDZs, bearing a similar substitution pattern to the 1,4-BDZs, have also been shown to behave as CCK_2 antagonists (Chart 2).[19] For instance, both enantiomers of 3-arylurea-containing compounds of this type, (+)-**4** and (−)-**4**, displayed selectivity for CCK_2 over CCK_1 receptors. Moreover, it had earlier been found that

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Chart 1. 1,4-BDZ-based CCK Antagonists

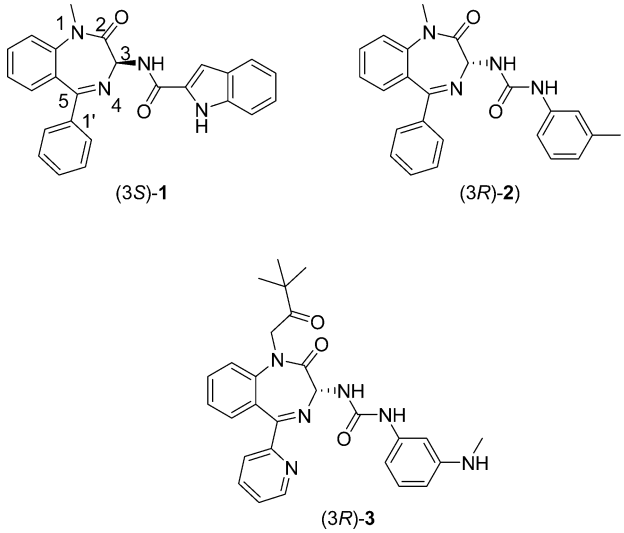
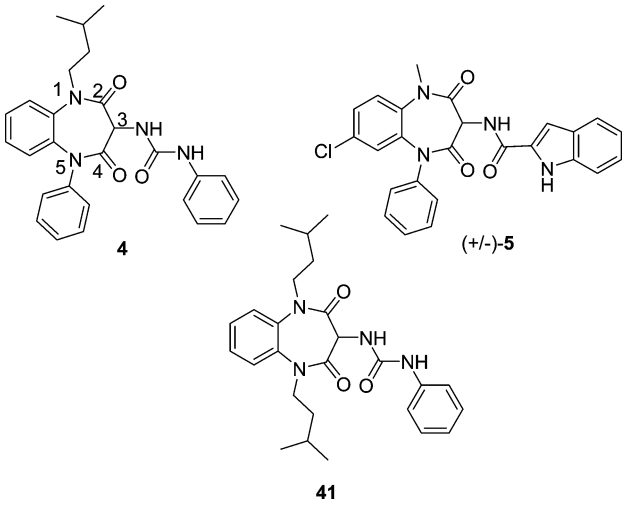


Table 1. Literature Affinity Values of Prototypical 1,4- and 1,5-BDZ-Based CCK Antagonists

compd	CCK_1	CCK_2	ref
(3*S*)-**1**	10.10[a]	6.57[b]	11
(3*R*)-**1**	8.08[a]	5.43[b]	11
(3*S*)-**2**	8.33[a]	6.55[b]	13
(3*R*)-**2**	6.13[a]	8.07[b]	13
(3*R*)-**3**	6.55[c]	10.17[d]	15
(3*S*)-**3**	4.89[c]	8.64[d]	15
(+)-**4**	5.34[e]	8.00[f]	19
(−)-**4**	6.74[e]	8.38[f]	19
(±)-**5**	7.70[a]	5.66[d]	20
41	7.21[e]	8.62[f]	24

[a] pIC_{50} for displacement of [^{125}I]-BH-CCK-8S from rat pancreas. [b] pIC_{50} for displacement of [^{125}I]-BH-CCK-8S from guinea pig cortex. [c] pK_I for displacement of [^{3}H]-L-364,718 from rat pancreas. [d] pK_I for displacement of [^{125}I]-BH-CCK-8S from rat cortex. [e] pK_I for displacement of [^{3}H]-CCK-8S from rat pancreas. [f] pK_I for displacement of [^{3}H]-CCK-8S from guinea pig cortex.

Chart 2. 1,5-BDZ-based CCK_2 Antagonists



the racemic 1,5-BDZ (±)-**5**, having a similar substitution pattern to **1**, showed higher affinity for CCK_1 than for CCK_2 receptors,[20] consistent with the receptor selectivity profile displayed by (3*S*)-**1** and (3*R*)-**1**, and provided strong support for the view that as far as their role as frameworks for obtaining CCK antagonists was concerned, the 1,4- and 1,5-BDZs were homologous.

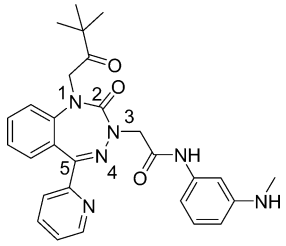


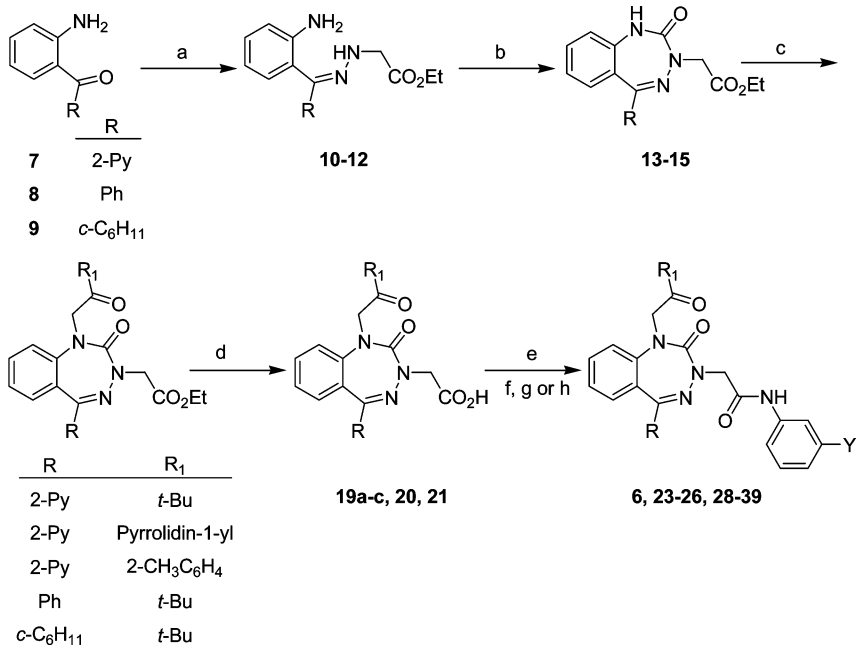
Figure 1. 1,3,4-Benzotriazepine-based analogue of (3*R*)-**3**.

Results and Discussion

Since CCK_2 receptor selectivity was favored in BDZs containing bulky substituents at the N-1 position regardless of the stereochemistry at the C-3 position, we considered that it might be possible to design achiral analogues of compounds such as (3*R*)-**3** that were CCK_2 antagonists and which maintained selectivity over CCK_1 receptors. We approached this by substituting a nitrogen atom for the chiral C-3 carbon. To avoid the presence of a further N−N bond and to retain the spatial relationship between the ring system and the aryl side chain, the urea nitrogen was also replaced with a methylene group to afford the novel 1,3,4-benzotriazepine **6** in which the 3-aryl substituent was attached by an acetamide link (Figure 1).

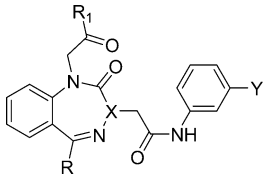
Compound **6** was prepared by the general route outlined in Scheme 1 and displayed moderate affinity for CCK_2 receptors, as judged by its displacement of [^{125}I]-BH-CCK-8S in a recombinant, human CCK_2 receptor radioligand binding assay, as well as by its inhibition of pentagastrin-stimulated acid secretion in an isolated, perfused rat stomach in vitro bioassay (Table 2). Although **6** was approximately 1000-fold less potent than (3*R*)-**3** at CCK_2 receptors, its selectivity over CCK_1 receptors was apparent from the lower affinity determined in a recombinant, human CCK_1 receptor radioligand binding assay. It was evident that for the 1,3,4-benzotriazepine ring system to reliably mimic a 1,4-BDZ, the N-3 nitrogen had to adopt a pyramidal rather than a planar geometry. This would enable **6** to access conformations, via pyramidal and ring inversion, equivalent to those adopted by both enantiomers of the corresponding 1,4-BDZ, (3*R*)-**3** and (3*S*)-**3**. The only X-ray structure available of a 1,3,4-benzotriazepine ring was that of **40**, which lacks substituents on the N-1 and N-3 positions (Figure 2).[21] Therefore, we determined the single-crystal X-ray structure of an N^1,N^3-substituted 1,3,4-benzotriazepine (**19a**) that was prepared as an intermediate in the synthesis of **6** (Figure 3)**.** In this structure, the triazepine ring was found to adopt a pseudoboat conformation and the internal bond angle around the N-3 nitrogen ((O)C^2−N^3−N^4═) of 116° was narrower than that determined in the X-ray structure of **40** (125°). Although this angle was larger in size than the corresponding angle ((O)C^2−C^3−N^4═) in the X-ray structures of representative 3*R* and 3*S* 1,4-BDZ-based CCK antagonists,[11,22] in most respects the conformations of the respective ring systems were broadly alike. Moreover, examination of the key parameters used to illustrate the similarity in conformation among the X-ray structures of 1,4-BDZs[23] (Table 3) indicates that, apart from θ_3, the corresponding values for **19a** all fall within the expected ranges. The smaller value of θ_3 for **19a** reflects the marginally lower bow of the pseudoboat conformation relative to (3*S*)-**1**. Nevertheless, since the acetate substituent at the N-3 position in **19a** occupies a pseudoequatorial position, superimposition of this X-ray structure on those of the 1,4-BDZ-based CCK antagonists shows good correspondence in conformation and side chain disposition (Figure 4).

Scheme 1. Synthesis of 1,3,4-Benzotriazepines[a]



[a] (a) $NH_2NHCH_2CO_2Et$·HCl/EtOH; (b) $(Cl_3CO)_2CO$, NEt_3/CH_2Cl_2; (c) R_1COCH_2Br, NaH/DMF; (d) NaOH/EtOH−H_2O; (e) $H_2NC_6H_4Y'$ (**22a**−**m**), EDC, 1-HOBt, DMAP/DMF; (f) CF_3CO_2H/CH_2Cl_2 (**6**, **23**−**26**, **29**, **32, 33**); (g) K_2CO_3, H_2O/THF−MeOH (**38**); (h) LiOH/THF−H_2O (**39**).

Table 2. Biological Data for 1,3,4-Benzotriazepine-Based CCK_2 Antagonists



cmpd	X	R	R_1	Y	CCK_2[a]	CCK_2[b]	CCK_1[c]
(3*S*)-**1**					6.14 ± 0.19	7.29 ± 0.16	10.63 ± 0.09[d]
(3*R*)-**2**					7.54 ± 0.03	8.11 ± 0.13	6.76 ± 0.04[d]
(3*R*)-**3**					10.10 ± 0.09	9.86 ± 0.13	7.52 ± 0.18[d]
6	N	2-Py	*t*-Bu	NHMe	6.65 ± 0.34	6.71 ± 0.04	22%[d]
23	N	2-Py	pyrrolidin-1-yl	NHMe	5.98 ± 0.27	5.60 ± 0.09	NT[e]
24	N	2-Py	$2\text{-}CH_3C_6H_4$	NHMe	7.30 ± 0.26	6.54 ± 0.01	NT[e]
25	N	Ph	*t*-Bu	NHMe	6.88 ± 0.29	7.13 ± 0.13	21%[d]
26	N	*c*-C_6H_{11}	*t*-Bu	NHMe	8.88 ± 0.14	8.10 ± 0.13	<5.0[d]
(3*S*)-**27**	CH	*c*-C_6H_{11}	*t*-Bu	NHMe	7.55 ± 0.40	8.22 ± 0.31	5.93 ± 0.11[d]
(3*R*)-**27**	CH	*c*-C_6H_{11}	*t*-Bu	NHMe	7.54 ± 0.41	7.88 ± 0.20	6.14 ± 0.05[d]
28	N	*c*-C_6H_{11}	*t*-Bu	NMe_2	7.04 ± 0.28	8.22 ± 0.11	16%[d]
29	N	*c*-C_6H_{11}	*t*-Bu	NH_2	7.44 ± 0.30	7.57 ± 0.11	40 ± 3%[f]
30	N	*c*-C_6H_{11}	*t*-Bu	pyrrolidin-1-yl	6.84 ± 0.26	7.80 ± 0.06	<5.0[d]
31	N	*c*-C_6H_{11}	*t*-Bu	morpholin-1-yl	7.74 ± 0.36	7.78 ± 0.07	42 ± 4%[f]
32	N	*c*-C_6H_{11}	*t*-Bu	$NH(CH_2)_2OCH_2CH_3$	6.98 ± 0.40	7.35 ± 0.18	<5.0[d]
33	N	*c*-C_6H_{11}	*t*-Bu	$NCH_3(CH_2)_2NHCH_3$	6.93 ± 0.40	7.53 ± 0.11	5.06 ± 0.06[f]
34	N	*c*-C_6H_{11}	*t*-Bu	imidazol-1-yl	6.06 ± 0.19	8.04 ± 0.06	57 ± 3%[f]
35	N	*c*-C_6H_{11}	*t*-Bu	Me	IA[g]	8.05 ± 0.15	27%[d]
36	N	*c*-C_6H_{11}	*t*-Bu	OMe	IA[g]	8.26 ± 0.17	46 ± 1%[f]
37	N	*c*-C_6H_{11}	*t*-Bu	OH	7.56 ± 0.32	7.88 ± 0.11	5.82 ± 0.05[f]
38	N	*c*-C_6H_{11}	*t*-Bu	CH_2OH	7.77 ± 0.28	7.82 ± 0.24	5.23 ± 0.07[d]
39	N	*c*-C_6H_{11}	*t*-Bu	CO_2H	9.01 ± 0.16	8.29 ± 0.05	4.95 ± 0.13[d]

[a] pA_2 ± SEM values, estimated from single shifts of pentagastrin concentration-effect curves in isolated, lumen-perfused immature rat stomachs. [b] pK_I ± SEM values obtained from competition with 20 pM [^{125}I]BH-CCK-8S for recombinant, human CCK_2 receptors expressed in NIH3T3 cell membranes from at least three separate experiments. [c] pK_I ± SEM values obtained from competition with 20 pM [^{3}H]-L-364,718 for recombinant, human CCK_1 receptors expressed in either PC3 or CHO cell membranes from at least three separate experiments. Where pK_I could not be determined, percentage inhibition at 10 μM from at least two separate experiments is recorded. [d] PC3 cell membranes. [e] Not tested. [f] CHO cell membranes. [g] Inactive at concentration tested (1×10^{-6} M).

With the preparation of **6**, our initial aim of obtaining a novel, achiral analogue of (3*R*)-**3** that was a selective CCK_2 antagonist had been met, and **6** was used as the starting point to obtain more potent compounds. This process was initially influenced by the structure−activity relationship (SAR) established during optimization of the 1,4-BDZ-based CCK_2 antagonists. Whereas variation in the nature of the substituent on the N-1 position (**23**, **24**) had little effect on receptor affinity, replacement of the C-5 pyrid-2-yl group in **6** by cyclohexyl (**26**) conferred significantly higher affinity. This was in contrast to the corresponding 5-phenyl substituted analogue (**25**) where the activity was unchanged with respect to **6**. The increase, which

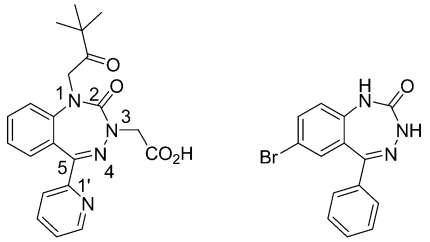


Figure 2. 1,3,4-Benzotriazepines used in a comparison of their X-ray structures with that of (3*S*)-**1**.

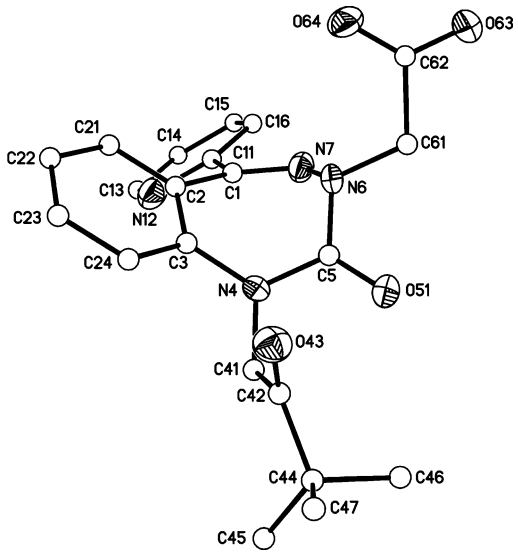


Figure 3. ORTEP perspective view of **19a** showing 30% probability displacement ellipsoids. The hydrogen atoms were omitted for clarity.

Table 3. Comparison of Geometrical Parameters[23] Derived from X-ray Structures of a 1,4-BDZ ((3*S*)-**1**)[32] and 1,3,4-Benzotriazepines (**19a** and **40**[33])

	θ_1 (deg)	θ_2 (deg)	θ_3 (deg)	Δ	$T_{(N1-C2)}$ (deg)	$L_{(N1-C2)}$ (Å)	$L_{(C5-C1')}$ (Å)	$T_{(C5-C1')}$ (deg)
(3*S*)-**1** (A)[a]	58	39	62	8.4	−12.5	1.36	1.52	−22, 158
(3*S*)-**1** (B)[a]	67	36	62	3.7	−5.8	1.40	1.47	−41, 141
19a	61	41	52	15.3	−25.7	1.39	1.52	−28, 153
40	64	36	43	18.1	−31.9	1.37	1.49	−42, 139

[a] Molecules A and B are the two independent molecules observed in the X-ray structure of **1**.[11]

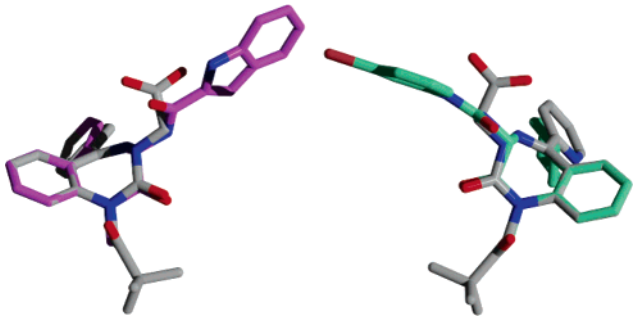


Figure 4. Superimposition of the X-ray structure of **19a** (white) with those of representative 3*S*[11] (purple) and 3*R*[22] (pale green) 1,4-BDZ-based CCK antagonists.

was achieved without altering the CCK_1 affinity, mirrored the higher affinity observed on making the corresponding change to (3*R*)-**2**.[22] In addition, it did not appear to be a result of perturbation of the 1,3,4-benzotriazepine ring conformation arising from replacement of the C-5 aryl group by cyclohexyl, since this remained unchanged in the X-ray structure of **21**, the 5-cyclohexyl analogue of **19a** (see Supporting Information). Although **26** was now closer in terms of CCK_2 affinity to (3*R*)-**3**, the possibility that the residual difference in affinity stemmed from the presence of the urea group linking the aromatic substituent to C-3 of the BDZ ring in (3*R*)-**3** or from an unfavorable receptor interaction with the additional ring nitrogen in **26** could not be discounted. The likelihood that the 1,3,4-benzotriazepine-based compounds bound to the CCK_2 receptor in a manner similar to their 1,4-BDZ counterparts was heightened with the preparation of (3*S*)-**27** and (3*R*)-**27**, the 1,4-BDZ C-3 acetamide analogues of **26**. While **26**, (3*S*)-**27**, and (3*R*)-**27** showed comparable affinity to one another at the human CCK_2 receptor, **26** achieved marginally higher affinity in the CCK_2 functional bioassay and relatively greater selectivity over CCK_1 receptors. This further illustration of enantiomers ((3*S*)-**27** and (3*R*)-**27**) of a 1,4-BDZ, containing bulky substituents at the N-1 position and displaying similar activity to one another, taken together with the data in Table 1 and the affinity of **26**, can be rationalized in at least one of two ways. It can be attributed to either the existence of distinct or overlapping binding sites for the separate enantiomers of a 1,4-BDZ (or the equivalent conformations of a 1,3,4-benzotriazepine) or a single binding site that can interact with both enantiomers of a 1,4-BDZ because of similar features in the nature of the binding pockets that accommodate the hydrophobic N-1 and C-5 substituents. Such a scenario would effectively allow the enantiomers to bind in the same region but upside down relative to one another. This latter prospect is consistent with the activity of the 1,5-BDZ **41** (Chart 2)[24] that is achiral by virtue of the symmetry of the ring and by having identical substituents at N-1 and N-5, which is as potent at CCK_2 receptors as the earlier chiral 1,5-BDZ-based CCK_2 antagonists (+)-**4** and (−)-**4**. As with the 1,3,4-benzotriazepines, **41** was prepared without the need for a resolution step.

Although **26** displayed high affinity at CCK_2 receptors, this compound lacked adequate aqueous solubility to satisfactorily evaluate its in vivo potency. A series of analogues (**28**−**34**) that contained other basic substituents in place of the methylamino group of **26** either failed to improve this property or were less potent. While compounds bearing methyl (**35**) and methoxy (**36**) substituents showed comparable affinity to **26** in the human CCK_2 receptor binding assay, they were inactive at the highest concentration tested in the functional bioassay. This difference in behavior of **35** and **36** across assays can be ascribed to low aqueous solubility. Accordingly, such compounds may be ineffective in the rat stomach assay since it is less tolerant than the radioligand binding assay of organic cosolvent that can be used to aid dissolution of compounds. The more polar hydroxyl (**37**) and hydroxymethyl (**38**) groups partially redressed this shortfall in affinity with respect to **26**, but parity in affinity to **26** in both CCK_2 assays was only achieved by introducing a carboxylic acid group (**39**) in this same position. Moreover, the aqueous solubility of **39** was significantly greater than that of **26**. Both acidic and basic derivatives of 1,4-BDZ-based CCK_2 antagonists have been observed previously,[14,25] not only strengthening the view that the 1,3,4-benzotriazepines share a similar mode of interaction with the CCK_2 receptor as the 1,4-BDZs but also strengthening the view that this substituent has little, if any, role in direct receptor interaction.

Careful consideration of the factors that govern receptor selectivity and affinity of 1,4-BDZ-based CCK ligands has made it possible to devise a series of novel achiral CCK_2 receptor antagonists, based on the rarely used 1,3,4-benzotriazepine ring

system. These compounds maintain a high preference for CCK_2 over CCK_1 receptors as judged by a comparison of their affinity in recombinant, human receptor radioligand binding assays. Moreover, **39** displays comparable affinity at the human CCK_2 receptor as at the canine CCK_2 receptor ($pK_I = 7.91 \pm 0.20$), and this combination of in vitro potency that is maintained across species and physicochemical properties identifies **39** as an attractive molecule for further SAR studies and for assessment of the in vivo activity of this class of compounds. This work will be covered in a separate publication.

Experimental Section

Flash column chromatography was performed on Merck silica gel 60 (40−63 μm) using the reported solvent systems. ^{1}H NMR spectra were recorded on a Bruker DRX-300 instrument at 300 MHz, and the chemical shifts (δ_H) were recorded relative to an internal standard.

(*N*′-((2-Amino-phenyl)-pyridin-2-yl-methylene)-hydrazino)-acetic Acid Ethyl Ester (10). A mixture of 2-aminophenyl(pyridin-2-yl)methanone (**7**)[26] (2.0 g, 10 mmol) and ethyl hydrazinoacetate HCl (2.0 g, 13 mmol) was heated at reflux in EtOH (20 mL) for 16 h. On cooling, the solvent was evaporated, and the residue was suspended in saturated $NaHCO_3$−EtOAc (1:1/120 mL). The organic phase was washed with brine (100 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent afforded the product as a yellow solid (3.54 g, 90%). ^{1}H NMR ($CDCl_3$) 8.59 (1H, dd), 7.60 (2H, m), 7.25 (1H, m), 7.14 (1H, m), 7.08 (1H, dd), 6.90−6.83 (2H, m), 6.03 (1H, t), 4.16 (4H, m), 3.94 (2H, br s), 1.27 (3H, t).

(*N*′-((2-Amino-phenyl)-phenyl-methylene)-hydrazino)-acetic Acid Ethyl Ester (11). Compound **11** was prepared by the same method used in the preparation of **10** except that 2-aminobenzophenone (**8**) was used in place of **7** (69%). ^{1}H NMR ($CDCl_3$) (1:1 mixture of *E/Z* isomers) 7.53 (2.5H, m), 7.35−7.27 (3H, m), 7.05 (1H, m), 6.87 (1H, m), 6.70 (1H, m), 6.48 (0.5H, m), 5.91 (1H, br s), 5.78 (0.5H, t), 5.43 (0.5H, t), 4.22−4.06 (3H, m), 3.95 (1H, d), 3.92 (1H, br s), 1.28 (3H, t).

(*N*′-((2-Amino-phenyl)-cyclohexyl-methylene)-hydrazino)-acetic Acid Ethyl Ester (12). Compound **12** was prepared by the same method used in the preparation of **10** except that (2-aminophenyl)cyclohexylmethanone (**9**)[27] was used in place of **7** (71%). ^{1}H NMR ($CDCl_3$) 7.17 (1H, dt), 6.98 (1H, dd), 6.80 (1H, dt), 6.73 (1H, dd), 5.32 (1H, t), 4.16 (2H, m), 3.95 (2H, br s), 3.89 (2H, m), 2.37 (1H, m), 1.80 (1H, m), 1.75−1.61 (4H, m), 1.33−1.19 (8H, m).

(2-Oxo-5-(pyridin-2-yl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (13). A solution of bis(trichloromethyl) carbonate (0.30 g, 1.0 mmol) in DCM[a] (5 mL) was added dropwise to a solution of **10** (0.79 g, 2.0 mmol) and NEt_3 (1.0 mL, 7.0 mmol) in DCM (10 mL) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 1 h and then washed with H_2O (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL). The organic phase was separated and dried over $MgSO_4$. Filtration and evaporation of the solvent gave the crude product which was purified by chromatography (EtOAc−DCM (1:1)) to yield the product as a yellow solid (0.67 g, 100%). ^{1}H NMR ($CDCl_3$) 8.63 (1H, m), 7.90 (1H, m), 7.78 (1H, m), 7.41−7.34 (2H, m), 7.11 (2H, m), 6.90 (1H, d), 6.81 (1H, s), 4.48 (2H, s), 4.23 (2H, q), 1.27 (3H, t).

(2-Oxo-5-phenyl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (14). Compound **14** was prepared by the same method used in the preparation of **13** except that **11** was used in place of **10** (38%). ^{1}H NMR ($CDCl_3$) 7.52−7.36 (6H, m), 7.10 (2H, m), 6.96 (2H, m), 4.48 (2H, s), 4.23 (2H, q), 1.27 (3H, t).

(5-Cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (15). Compound **15** was prepared by the same method used in the preparation of **13** except that **12** was used in place of **10** (62%). ^{1}H NMR ($CDCl_3$) 7.35 (2H, m), 7.12 (1H, t), 6.85 (2H, m), 4.32 (2H, s), 4.18 (2H, m), 2.68 (1H, m), 1.81−1.68 (5H, m), 1.49−1.22 (8H, m).

(1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-(pyridin-2-yl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (16a). To an ice-cooled solution of **13** (0.92 g, 2.84 mmol) in DMF (10 mL) was added NaH (60% dispersion in mineral oil, 0.14 g, 12.0 mmol) in small portions. The mixture was stirred at ambient temperature for 30 min, and then 1-bromo-3,3-dimethyl-butan-2-one (0.46 mL, 3.4 mmol) was added. The reaction mixture was stirred at ambient temperature for 2 h, diluted with H_2O (100 mL), and extracted with EtOAc (40 mL × 3). The combined extracts were washed with brine (40 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography ((EtOAc−DCM (3:7)) to afford the product as a yellow foam (0.75 g, 63%). ^{1}H NMR ($CDCl_3$) 8.63 (1H, m), 8.00 (1H, dd), 7.77 (1H, dt), 7.44 (1H, m), 7.30 (1H, m), 7.17 (2H, m), 7.03 (1H, d), 4.65 (2H, br s), 4.41 (2H, br s), 4.18 (2H, q), 1.24 (12H, m).

(1-(2-Oxo-2-pyrrolidin-1-yl-ethyl)-2-oxo-5-(pyridin-2-yl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (16b). Compound **16b** was prepared by the same method used in the preparation of **16a** except that 2-bromo-1-pyrrolidin-1-yl-ethanone[28] was used in place of 1-bromo-3,3-dimethyl-butan-2-one (26%). ^{1}H NMR ($CDCl_3$) 8.63 (1H, m), 7.98 (1H, m), 7.78 (1H, dt), 7.46 (2H, m), 7.32 (1H, m), 7.15 (2H, m), 4.40 (4H, m), 4.19 (2H, q), 3.53 (2H, m), 3.46 (2H, m), 1.97−1.81 (4H, m), 1.24 (3H, t).

(1-(2-Oxo-2-*o*-tolyl-ethyl)-2-oxo-5-(pyridin-2-yl)-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (16c). Compound **16c** was prepared by the same method used in the preparation of **16a** except that 2-bromo-1-*o*-tolyl-ethanone[29] was used in place of 1-bromo-3,3-dimethyl-butan-2-one (31%). ^{1}H NMR ($CDCl_3$) 8.64 (1H, d), 7.79 (1H, dt), 7.61 (1H, d), 7.49 (1H, dt), 7.34−7.16 (3H, m), 4.93 (2H, s), 4.42 (2H, br s), 4.19 (2H, q), 2.48 (3H, s), 1.24 (3H, t).

(1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-phenyl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (17). Compound **17** was prepared by the same method used in the preparation of **16a** except that **14** was used in place of **13** (61%). ^{1}H NMR ($CDCl_3$) 7.60 (2H, m), 7.43 (4H, m), 7.13 (2H, m), 7.04 (1H, d), 4.74 (2H, br s), 4.45 (2H, m), 4.18 (2H, q), 1.23 (12H, m).

(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (18). Compound **18** was prepared by the same method used in the preparation of **16a** except that **15** was used in place of **13** (84%). ^{1}H NMR ($CDCl_3$) 7.37 (2H, m), 7.17 (1H, dt), 6.93 (1H, d), 4.66 (2H, s), 4.35 (1H, m), 4.13 (3H, m), 2.74 (1H, m), 1.90−1.70 (6H, m), 1.31−1.16 (16H, m).

(1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid (19a). A solution of **16a** (0.74 g, 1.75 mmol) and 1.0 M NaOH (1.75 mL, 1.75 mmol) in EtOH (20 mL) was stirred at ambient temperature for 16 h. The mixture was concentrated under reduced pressure, diluted with H_2O (30 mL), and acidified to pH 3 with 1 N HCl. The mixture was extracted with DCM (30 mL × 2), and the combined extracts were dried over $MgSO_4$. Filtration and evaporation of the solvent afforded the product as a pale yellow foam (0.7 g, 100%). ^{1}H NMR (DMSO-d_6) 12.50 (1H, br s), 8.57 (1H, m), 7.94 (2H, m), 7.50 (2H, m), 7.16 (3H, m), 4.78 (2H, s), 4.25 (2H, br s), 1.15 (9H, s).

(1-(2-Oxo-2-pyrrolidin-1-yl-ethyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid (19b). Compound **19b** was prepared by the same method used in the preparation of **19a** except that **16b** was used in place of **16a** (95%). ^{1}H NMR ($CDCl_3$) 8.65 (1H, dd), 7.93 (1H, d), 7.79 (1H, dt), 7.47 (2H, m), 7.36 (1H, m), 7.16 (2H, m), 4.34 (4H, br s), 3.54 (2H, br s), 3.45 (2H, br s), 1.94 (2H, m), 1.84 (2H, m).

(1-(2-Oxo-2-*o*-tolyl-ethyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid (19c). Compound **19c** was prepared by the same method used in the preparation of **19a**

[a] Abbreviations: DCM, dichloromethane; THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide; DMAP, 4-(dimethylamino)pyridine; EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl; HOBt, 1-hydroxybenzotriazole; EEDQ, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline.

except that **16c** was used in place of **16a** (99%). ^{1}H NMR ($CDCl_3$) 8.66 (1H, d), 8.49 (1H, d), 7.77 (2H, d), 7.64−7.12 (8H, m), 4.95 (2H, s), 4.37 (2H, s), 2.45 (3H, s).

(1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-phenyl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid (20). Compound **20** was prepared by the same method used in the preparation of **19a** except that **17** was used in place of **16a** (96%). ^{1}H NMR ($CDCl_3$) 7.62 (2H, m), 7.47 (4H, m), 7.19 (2H, m), 7.06 (1H, d), 4.75 (2H, m), 4.25 (2H, m), 1.25 (9H, s).

(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid (21). Compound **21** was prepared by the same method used in the preparation of **19a** except that **18** was used in place of **16a** (95%). ^{1}H NMR ($CDCl_3$) 11.00 (1H, br s), 7.45 (2H, m), 7.25 (1H, m), 6.97 (1H, dd), 4.68 (2H, m), 4.25 (1H, d), 3.90 (1H, d), 2.80 (1H, m), 2.08−1.61 (6H, m), 1.44−1.18 (13H, m).

(3-Amino-phenyl)-methyl-carbamic Acid *tert*-Butyl Ester (22a). Step A. A solution of 3-nitrophenyl isocyanate (14.44 g, 88.0 mmol) in *tert*-butyl alcohol (80 mL) was heated at reflux for 2 h. On cooling, the solvent was evaporated, and the residue was dried under high vacuum and washed thoroughly with Et_2O to afford (3-nitro-phenyl)-carbamic acid *tert*-butyl ester as a yellow solid (19.96 g, 95%). ^{1}H NMR ($CDCl_3$) 8.30 (1H, s), 7.88 (1H, d), 7.71 (1H, d), 7.45 (1H, t), 6.68 (1H, br s), 1.55 (9H, s).

Step B. To an ice-cooled solution of (3-nitro-phenyl)-carbamic acid *tert*-butyl ester (3.57 g, 15.0 mmol) in DMF (30 mL) was added NaH (60% dispersion in mineral oil, 720 mg, 18.0 mmol) in small portions. After stirring at ambient temperature for 1 h, the reaction mixture was cooled externally with ice, and iodomethane (1.4 mL, 22.5 mmol) was added. The reaction mixture was stirred at ambient temperature for 2 h, diluted with H_2O (150 mL), and extracted with EtOAc (50 mL × 2). The combined extracts were washed with brine and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by chromatography (EtOAc−DCM (1:9)) to afford methyl-(3-nitro-phenyl)-carbamic acid *tert*-butyl ester as a yellow foam (3.34 g, 88%). ^{1}H NMR ($CDCl_3$) 8.16 (1H, t), 8.00 (1H, m), 7.63 (1H, m), 7.48 (1H, t), 3.34 (3H, s), 1.49 (9H, s).

Step C. A round-bottom flask containing methyl-(3-nitro-phenyl)-carbamic acid *tert*-butyl ester (3.30 g, 13.1 mmol), 10% palladium on charcoal (300 mg), and THF−MeOH (1:1/50 mL) was evacuated and flushed with hydrogen three times. The mixture was stirred vigorously overnight under an atmosphere of hydrogen. The catalyst was removed by filtration through a pad of Celite, and the filtrate evaporated to afford **22a** as a white solid (2.90 g, 99%). ^{1}H NMR ($CDCl_3$) 7.10 (1H, t), 6.62 (2H, m), 6.50 (1H, m), 3.66 (2H, br s), 3.22 (3H, s), 1.46 (9H, s).

(3-Amino-phenyl)-carbamic Acid *tert*-Butyl Ester (22c). Compound **22c** was prepared using step C of the method of preparation of **22a** except that (3-nitro-phenyl)-carbamic acid *tert*-butyl ester was used in place of methyl-(3-nitro-phenyl)-carbamic acid *tert*-butyl ester (100%). ^{1}H NMR ($CDCl_3$) 7.03 (2H, m), 6.56 (1H, m), 6.37 (1H, m), 3.65 (2H, m), 1.50 (9H, s).

3-Morpholin-4-yl-phenylamine (22e). Step A. A mixture of morpholine (13.1 mL, 0.15 mol) and 3-fluoro-nitrobenzene (3.2 mL, 30 mmol) in DMSO (25 mL) was heated at 100 °C for 18 h. On cooling, the mixture was poured into H_2O (300 mL). The precipitated solid was isolated by filtration and washed with H_2O to afford 4-(3-nitrophenyl)morpholine (4.6 g, 74%). ^{1}H NMR ($CDCl_3$) 7.70 (2H, m), 7.40 (1H, t), 7.19 (1H, m), 3.88 (4H, m), 3.25 (4H, m).

Step B. Compound **22e** was prepared using step C of the method of preparation of **22a** except that 4-(3-nitrophenyl)morpholine was used in place of methyl-(3-nitro-phenyl)-carbamic acid *tert*-butyl ester (90%). ^{1}H NMR ($CDCl_3$) 7.06 (1H, m), 6.35 (1H, m), 6.24 (2H, m), 3.84 (4H, m), 3.62 (2H, m), 3.13 (4H, m).

(3-Amino-phenyl)-2-ethoxyethyl-carbamic Acid *tert*-Butyl Ester (22f). Compound **22f** was prepared by the same method used in the preparation of **22a** except that 2-bromoethyl-ethyl ether was used in step B in place of iodomethane (100%). ^{1}H NMR ($CDCl_3$) 7.09 (1H, t), 6.62 (2H, m), 6.52 (1H, d), 3.75 (2H, m), 3.64 (2H, br s), 3.55 (2H, m), 3.47 (2H, q), 1.45 (9H, s), 1.74 (3H, t).

(2-((3-Amino-phenyl)-methyl-amino)-ethyl)-methyl-carbamic Acid *tert*-Butyl Ester (22g). Step A. A mixture of 3-fluoro-nitrobenzene (1.00 g, 7.1 mmol) in *N*,*N*′-dimethylethylenediamine (10 mL) was heated at reflux for 18 h. On cooling, the mixture was acidified to pH 2 with 2 N HCl and washed with Et_2O (100 mL). The mixture was basified to pH 11 with 10% Na_2CO_3 and extracted with DCM (2 × 75 mL). The extracts were washed with brine (2 × 100 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by chromatography (NH_4OH−MeOH−DCM (0.1:1:10)) to yield *N*-methyl-*N*-(2-(methylamino)ethyl)-3-nitrobenzenamine (0.84 g, 57%). ^{1}H NMR ($CDCl_3$) 7.53−7.49 (2H, m), 7.35−7.29 (1H, m), 7.03−6.99 (1H, m), 3.55−3.47 (2H, m), 3.05 (3H, s), 2.86−2.81 (2H, m), 2.49 (3H, s), 1.16 (1H, br s).

Step B. A solution of *N*-methyl-*N*-(2-(methylamino)ethyl)-3-nitrobenzenamine (0.84 g, 4.0 mmol), di-*tert*-butyl dicarbonate (1.32 g, 6.1 mmol), and DMAP (5 mg) in DCM (20 mL) was stirred at ambient temperature for 2 h. The mixture was diluted with DCM (30 mL), washed with 5% $KHSO_4$ (40 mL) and saturated $NaHCO_3$ solution (40 mL), and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by chromatography (EtOAc−hexanes (1:2)) to yield *N*-*tert*-butoxy-carbonyl-*N*-methyl-*N*-(2-(methylamino)ethyl)-3-nitrobenzenamine (0.94 g, 75%). ^{1}H NMR ($CDCl_3$) 7.52−7.49 (2H, m), 7.35−7.30 (1H, m), 7.00 (1H, br s), 3.56 (2H, br s), 3.43−3.39 (2H, m), 3.05 (3H, s), 2.90−2.82 (3H, m), 1.42 (9H, s).

Step C. Compound **22g** was prepared using step C of the method of preparation of **22a** except that *N*-*tert*-butoxycarbonyl-*N*-methyl-*N*-(2-(methylamino)ethyl)-3-nitrobenzenamine was used in place of methyl-(3-nitro-phenyl)-carbamic acid *tert*-butyl ester (58%). ^{1}H NMR ($CDCl_3$) 7.01 (1H, t, J = 8.1 Hz), 6.20−6.19 (1H, m), 6.09−6.04 (2H, m), 3.57 (2H, br s), 3.44−3.34 (4H, m), 2.92−2.85 (6H, m), 1.47 (9H, s).

3-Aminobenzyl Methyl Carbonate (22l). Step A. Methyl chloroformate (0.85 mL, 11 mmol) was added dropwise to a solution of 3-nitrobenzyl alcohol (1.53 g, 10 mmol) in pyridine−DCM (1:10/27.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to ambient temperature, and stirred for 1 h. The solution was washed with 2 N HCl (2 × 20 mL) and H_2O (30 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave carbonic acid 3-nitrobenzyl methyl carbonate as a white solid (1.94 g, 92%). ^{1}H NMR ($CDCl_3$) 8.26 (1H, s), 8.21 (1H, d), 7.72 (1H, d), 7.56 (1H, t), 5.25 (2H, s), 3.83 (3H, s).

Step B. A mixture of $SnCl_2 \cdot H_2O$ (10.3 g, 46 mmol) and 3-nitrobenzyl methyl carbonate (1.93 g, 9.1 mmol) in EtOAc (50 mL) was heated at reflux under argon for 1 h. On cooling, the solution was poured into a 5% $NaHCO_3$ solution (200 mL). The mixture was diluted with EtOAc (100 mL), and the organic layer was separated and dried ($MgSO_4$). Filtration and evaporation of the solvent gave **22l** as a yellow oil (1.46 g, 89%). ^{1}H NMR ($CDCl_3$) 7.15 (1H, t), 6.76 (1H, d), 6.70 (1H, s), 6.65 (1H, dd), 5.08 (2H, s), 3.80 (3H, s), 3.69 (2H, br s).

2-(1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-methylamino-phenyl)-acetamide (6). Step A. Compound **22a** (0.18 g, 0.81 mmol) was added to a solution of **19a** (0.32 g, 0.81 mmol), HOBt (0.17 g, 1.2 mmol), DMAP (1 mg), and EDCI (0.23 g, 1.2 mmol) in DMF (5 mL). The solution was maintained at ambient temperature for 16 h, diluted with H_2O (30 mL), and extracted with EtOAc (20 mL × 2). The combined extracts were washed with 5% $KHSO_4$ (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by chromatography (EtOAc−DCM (1:4)) to afford (3-(2-(5-pyridin-2-yl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-methyl-carbamic acid *tert*-butyl ester as a yellow foam (0.36 g, 75%). ^{1}H NMR ($CDCl_3$) 8.63 (1H, d), 8.25 (1H, s), 8.11 (1H, d), 7.80 (1H, dt), 7.55 (1H, t), 7.45 (1H, s), 7.38−7.27 (3H, m), 7.18 (2H,

d), 7.12 (1H, d), 6.94 (1H, m), 4.70 (2H, s), 4.44 (2H, s), 3.21 (3H, s), 1.42 (9H, s), 1.26 (9H, s).

Step B. A solution of (3-(2-(5-pyridin-2-yl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-methyl-carbamic acid *tert*-butyl ester (0.11 g, 0.18 mmol) in trifluoroacetic acid (3 mL) was stirred at ambient temperature for 1 h. The reaction mixture was evaporated to dryness, and the residue was suspended in saturated $NaHCO_3$−EtOAc (1:1/40 mL). The organic phase was separated and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by chromatography (EtOAc−DCM (1:4)) to afford **6** as a colorless foam (44 mg, 49%). ^{1}H NMR ($CDCl_3$) 8.62 (1H, d), 8.10 (1H, d), 8.00 (1H, br s), 7.79 (1H, dt), 7.55 (1H, m), 7.29 (3H, m), 7.13 (1H, d), 7.01 (1H, t), 6.92 (1H, t), 6.48 (1H, dd), 6.30 (1H, dd), 4.68 (2H, br d), 4.45 (2H, br d), 2.80 (1H, br s), 2.78 (3H, s), 1.27 (9H, s). Anal. ($C_{28}H_{30}N_6O_3$) C, H, N.

***N*-(3-Methylamino-phenyl)-2-(2-oxo-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetamide (23).** Compound **23** was prepared by the same method used in the preparation of **6** except that **19b** was used in place of **19a** in step A (73%). ^{1}H NMR ($CDCl_3$) 8.61 (1H, d), 8.07 (2H, m), 7.77 (1H, dt), 7.54 (2H, m), 7.36−7.24 (3H, m), 6.98 (1H, t), 6.88 (1H, s), 6.48 (1H, d), 6.28 (1H, d), 4.53−4.34 (4H, br m), 3.52−3.20 (5H, br m), 2.75 (3H, s), 1.97 (2H, m), 1.87 (2H, m). Anal. ($C_{28}H_{29}N_7O_3 \cdot 0.3H_2O$) C, H, N.

***N*-(3-Methylamino-phenyl)-2-(2-oxo-1-(2-oxo-2-*o*-tolyl-ethyl)-5-pyridin-2-yl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetamide (24).** Compound **24** was prepared by the same method used in the preparation of **6** except that **19c** was used in place of **19a** in step A (36%). ^{1}H NMR ($CDCl_3$) 8.64 (1H, d), 8.08 (1H, d), 8.03 (1H, s), 7.79 (1H, dt), 7.59 (2H, m), 7.39−7.26 (5H, m), 7.19 (2H, m), 7.01 (1H, t), 6.90 (1H, s), 6.47 (1H, dd), 6.30 (1H, dd), 4.98 (2H, s), 4.45 (2H, br m), 3.30 (1H, br s), 2.76 (3H, s), 2.47 (3H, s). Anal. ($C_{31}H_{28}N_6O_3$) C, H, N.

2-(1-(3,3-Dimethyl-2-oxo-butyl)-2-oxo-5-phenyl-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-methylamino-phenyl)-acetamide (25). Compound **25** was prepared by the same method used in the preparation of **6** except that **20** was used in place of **19a** in step A (87%). ^{1}H NMR ($CDCl_3$) 8.01 (1H, s), 7.63 (2H, m), 7.55 (1H, m), 7.42 (3H, m), 7.25 (2H, m), 7.14 (1H, d), 7.00 (1H, t), 6.90 (1H, t), 6.40 (1H, dd), 6.29 (1H, dd), 4.76 (2H, m), 4.52 (1H, d), 4.34 (1H, d), 3.25 (1H, br s), 2.77 (3H, s), 1.26 (9H, s). Anal. ($C_{29}H_{31}N_5O_3 \cdot 0.5H_2O$) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-methylamino-phenyl)-acetamide (26). Compound **26** was prepared by the same method used in the preparation of **6** except that **21** was used in place of **19a** in step A (65%). ^{1}H NMR ($CDCl_3$) 8.07 (1H, s), 7.48 (2H, m), 7.27 (1H, dt), 7.04 (2H, m), 6.91 (1H, t), 6.46(1H, dd), 6.31 (1H, dd), 4.68 (2H, m), 4.35 (1H, d), 4.13 (1H, d), 3.72 (1H, br s), 2.80 (4H, m), 2.05−1.72 (6H, m), 1.27 (13H, m). Anal. ($C_{29}H_{37}N_5O_3$) C, H, N.

2-((*S*)-5-Cyclohexyl-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-2-oxo-1*H*-benzo[*e*][1,4]diazepin-3-yl)-*N*-(3-(methylamino)phenyl)-acetamide ((3*S*)-27). Step A. A solution of **9** (2.52 g, 12 mmol), L-*N*-boc-*β*-benzyl aspartic acid (4.0 g, 12 mmol), and EEDQ (3.06 g, 12 mmol) in DCM (40 mL) was stirred at ambient temperature for 24 h. The solution was diluted with DCM (60 mL), washed with 2 N HCl (2 × 50 mL), and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by chromatography (EtOAc−hexanes (3:10)) to give *tert*-butyl (*S*)-2-((benzyloxy)carbonyl)-1-((2-cyclohexylcarbonyl)phenylcarbamoyl)-ethylcarbamate as a yellow oil (5.76 g, 91%). ^{1}H NMR ($CDCl_3$) 12.49 (1H, s), 8.75 (1H, d), 7.91 (1H, d), 7.52 (1H, t), 7.35−7.30 (5H, m), 7.13 (1H, t), 5.80 (1H, t), 5.15 (2H, dd), 4.75 (1H, m), 3.30 (2H, m), 2.85 (1H, m), 1.90−1.70 (4H, m), 1.65−1.20 (16H, m). $[\alpha]^{25}_D$ 0.0° (*c* 1.0, DCM).

Step B. (*S*)-Benzyl 3-((2-cyclohexylcarbonyl)phenylcarbamoyl)-3-aminopropanoate was prepared using step B of the preparation of **6** except that *tert*-butyl (*S*)-2-((benzyloxy)carbonyl)-1-((2-cyclohexylcarbonyl)phenylcarbamoyl)ethylcarbamate was used in place of (3-(2-(5-pyridin-2-yl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-methyl-carbamic acid *tert*-butyl ester (99%). ^{1}H NMR ($CDCl_3$) 12.60 (1H, br s), 8.77 (1H, d, J = 8.6 Hz), 7.92 (1H, d, J = 8.0 Hz), 7.53 (1H, dd, J = 7.8, 7.8 Hz), 7.36−7.31 (5H, m), 7.15 (1H, dd, J = 7.8, 7.8 Hz), 5.18 (1H, d, J = 12.3 Hz), 5.13 (1H, d, J = 12.3 Hz), 4.14 (1H, m), 3.88 (1H, m), 3.32 (1H, m), 3.04 (1H, dd, J = 16.5, 3.9 Hz), 2.83 (1H, dd, J = 16.5, 8.1 Hz), 1.89−1.77 (7H, m), 1.55−1.37 (5H, m). $[\alpha]^{25}_D$ +11.5° (*c* 2.0, $CDCl_3$).

Step C. A solution of (*S*)-benzyl 3-((2-cyclohexylcarbonyl)-phenylcarbamoyl)-3-aminopropanoate (4.53 g, 11 mmol) and ammonium acetate (4.27 g, 55 mmol) in acetic acid (80 mL) was stirred at ambient temperature for 24 h. The solvent was evaporated and the residue suspended in EtOAc-saturated $NaHCO_3$ (1:1/500 mL). The organic layer was separated, washed with saturated $NaHCO_3$ (100 mL), and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by chromatography (EtOAc−hexanes (3:5)) to give benzyl 2-((*S*)-5-cyclohexyl-2,3-dihydro-2-oxo-1*H*-benzo[*e*][1,4]diazepin-3-yl)acetate as a colorless oil (3.34 g, 77%). ^{1}H NMR ($CDCl_3$) 7.82 (1H, s), 7.57 (1H, d, J = 7.8 Hz), 7.43 (1H, dd, J = 7.8 Hz, 7.8 Hz), 7.34−7.22 (6H, m), 7.00 (1H, dd, J = 8.1 Hz, 0.9 Hz), 5.15 (1H, d, J = 13.3 Hz), 5.13 (1H, d, J = 13.3 Hz), 4.01 (1H, t, J = 6.9 Hz), 3.35 (1H, dd, J = 16.5 Hz, 7.2 Hz), 3.25 (1H, m), 1.90−1.75 (2H, m), 1.67−1.40 (4H, m), 1.35−1.05 (4H, m). $[\alpha]^{25}_D$ −2.0° (*c* 1.0, $CHCl_3$).

Step D. Benzyl 2-((*S*)-5-cyclohexyl-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-2-oxo-1*H*-benzo[*e*][1,4]diazepin-3-yl)acetate was prepared by the same method used in the preparation of **16a** except that benzyl 2-((*S*)-5-cyclohexyl-2,3-dihydro-2-oxo-1*H*-benzo[*e*][1,4]-diazepin-3-yl)acetate was used in place of **13** (61%). ^{1}H NMR ($CDCl_3$) 7.52 (1H, dd, J = 7.8 Hz, 1.5 Hz), 7.41 (1H, dd, J = 7.8 Hz, 7.8 Hz), 7.33−7.23 (6H, m), 7.03 (1H, dd, J = 8.1 Hz, 0.9 Hz), 5.11 (2H, s), 4.88 (1H, d, J = 17.7 Hz), 4.55 (1H, d, J = 17.7 Hz), 4.09 (1H, m), 3.22 (1H, dd, J = 16.5 Hz, 9.0 Hz), 3.17 (1H, dd, J = 16.5 Hz, 7.5 Hz), 2.77 (1H, m), 1.87−1.56 (5H, m), 1.29−1.16 (14H, m). $[\alpha]^{25}_D$ +69.0° (*c* 1.0, $CHCl_3$).

Step E. A solution of benzyl 2-((*S*)-5-cyclohexyl-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-2-oxo-1*H*-benzo[*e*][1,4]diazepin-3-yl)-acetate (2.50 g, 5.1 mmol) and 2.05 M NaOH (10 mL, 20.5 mmol) in EtOH (10 mL) was heated at 60 °C for 30 min. The solvent was evaporated under reduced pressure, and the residue was diluted with H_2O (30 mL) and acidified to pH 1 with 2 N HCl. The mixture was extracted with EtOAc (50 mL × 3), and the combined extracts were dried over $MgSO_4$. Filtration and evaporation of the solvent gave the crude product which was purified by chromatography (EtOAc) to afford 2-((*S*)-5-cyclohexyl-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-2-oxo-1*H*-benzo[*e*][1,4]diazepin-3-yl)acetic acid as a pale yellow solid (1.23 g, 60%). ^{1}H NMR ($CDCl_3$) 12.20 (1H, br s), 7.60 (1H, dd, J = 7.8 Hz, 1.5 Hz), 7.50 (1H, t, J = 7.2 Hz), 7.48−7.28 (1H, m), 7.06 (1H, d, J = 8.4 Hz), 4.97 (1H, d, J = 18.0 Hz), 4.50 (1H, d, J = 17.7 Hz), 3.96 (1H, t, J = 4.7 Hz), 3.06 (1H, dd, J = 16.1 Hz, 4.1 Hz), 2.90 (1H, m), 2.81 (1H, dd, J = 16.1 Hz, 5.6 Hz), 2.05 (1H, m), 1.85 (1H, m), 1.75−1.66 (4H, m), 1.36−1.19 (13H, m). $[\alpha]^{25}_D$ +138.0° (*c* 1.0, $CDCl_3$).

Step F. Compound (3*S*)-**27** was prepared by the same method used in the preparation of **6** except that 2-((*S*)-5-cyclohexyl-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-2-oxo-1*H*-benzo[*e*][1,4]diazepin-3-yl)acetic acid was used in place of **19a** in step A (71%). The compound was further characterized as the HCl salt. ^{1}H NMR (DMSO-d_6) 10.43 (1H, s), 7.79−7.76 (2H, m), 7.60 (1H, t, J = 8.4 Hz), 7.40−7.33 (4H, m), 7.07 (1H, d, J = 8.4 Hz), 4.92 (2H, s), 4.04 (1H, t, J = 7.5 Hz), 3.11 (2H, m), 3.00 (1H, m), 2.82 (3H, s), 1.85 (1H, m), 1.75 (1H, m), 1.66−1.50 (4H, m), 1.40−1.11 (13H, m). $[\alpha]^{25}_D$ +23.0° (*c* 1.0, DMSO-d_6). Anal. ($C_{30}H_{38}N_4O_3 \cdot HCl \cdot 3.5H_2O$) C, H, N.

2-((*R*)-5-Cyclohexyl-2,3-dihydro-1-(3,3-dimethyl-2-oxobutyl)-2-oxo-1*H*-benzo[*e*][1,4]diazepin-3-yl)-*N*-(3-(methylamino)phenyl)-acetamide ((3*R*)-27). Compound (3*R*)-**27** was prepared by the method used in the preparation of (3*S*)-**27** except that D-*N*-boc-*β*-benzyl aspartic acid was used in place of L-*N*-boc-*β*-benzyl aspartic acid in step A (99%). ^{1}H NMR (DMSO-d_6) 10.43 (1H, s), 7.79−

7.76 (2H, m), 7.60 (1H, t, J = 8.4 Hz), 7.40−7.33 (4H, m), 7.07 (1H, d, J = 8.4 Hz), 4.92 (2H, s), 4.04 (1H, t, J = 7.5 Hz), 3.11 (2H, m), 3.00 (1H, m), 2.82 (3H, s), 1.85 (1H, m), 1.75 (1H, m), 1.66−1.50 (4H, m), 1.40−1.11 (13H, m). $[\alpha]^{25}_{D}$ −21.0° (*c* 1.0, DMSO-d_6). Anal. ($C_{30}H_{38}N_4O_3$·HCl·3.5H_2O) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-(dimethylamino)-phenyl)-acetamide (28). Compound **28** was prepared using step A of the method of preparation of **6** except that **21** and *m*-*N*,*N*-dimethylaminoaniline **(22b)** were used in place of **19a** and **22a**, respectively, in step A (39%). ^{1}H NMR ($CDCl_3$) 8.08 (1H, s), 7.50 (2H, m), 7.28 (1H, m), 7.10 (2H, m), 6.88 (1H, m), 6.64 (1H, m), 6.45 (1H, m), 4.69 (1H, d), 4.67 (1H, d), 4.36 (1H, d), 4.14 (1H, d), 2.95 (6H, m), 2.74 (1H, m), 2.00−1.71 (6H, m), 1.36−1.17 (13H, m). The compound was further characterized as the HCl salt. Anal. ($C_{30}H_{39}N_5O_3$·HCl·2.0H_2O) C, H, N.

***N*-(3-Amino-phenyl)-2-(5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetamide (29).** Compound **29** was prepared by the same method used in the preparation of **6** except that **21** and **22c** were used in place of **19a** and **22a**, respectively, in step A (37%). ^{1}H NMR ($CDCl_3$) 11.28 (1H, br s), 8.85 (1H, s), 7.69 (1H, s), 7.57−7.27 (6H, m), 7.04 (1H, m), 4.76 (1H, d), 4.63 (1H, d), 4.21 (2H, m), 2.80 (1H, m), 2.18−1.35 (6H, m), 1.32−1.22 (13H, m). The product was further characterized as the HCl salt. Anal. ($C_{28}H_{35}N_5O_3$·HCl·2.0H_2O) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-pyrrolidin-1-yl-phenyl)-acetamide (30). Compound **30** was prepared using step A of the method of preparation of **6** except that **21** and 3-pyrrolidin-1-yl-phenylamine (**22d**)[30] were used in place of **19a** and **22a**, respectively (63%). ^{1}H NMR ($CDCl_3$) 8.01 (1H, s), 7.49 (2H, m), 7.24 (1H, m), 7.04 (2H, m), 6.72 (1H, s), 6.51 (1H, d), 6.26 (1H, d), 4.69 (2H, m), 4.42 (1H, d), 4.12 (1H, d), 3.25 (4H, m), 2.77 (1H, m), 2.00−1.69 (10H, m), 1.28−1.21 (13H, m). The compound was further characterized as the HCl salt. Anal. ($C_{32}H_{41}N_5O_9$·HCl) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-morpholin-4-yl-phenyl)-acetamide (31). Compound **31** was prepared using step A of the method of preparation of **6** except that **21** and **22e** were used in place of **19a** and **22a**, respectively (88%). ^{1}H NMR ($CDCl_3$) 8.22 (1H, br s), 7.50−7.44 (2H, m), 7.29−7.12 (3H, m), 7.03 (1H, d, J = 8.1 Hz), 6.75 (1H, d, J = 8.1 Hz), 6.63−6.60 (1H, m), 4.77 (1H, d, J = 17.7 Hz), 4.65 (1H, d, J = 17.7 Hz), 4.34 (1H, d, J = 16.8 Hz), 4.19 (1H, d, J = 16.8 Hz), 3.84 (4H, t, J = 4.8 Hz), 3.15 (4H, t, J = 4.8 Hz), 2.82−2.75 (1H, m), 2.05−1.74 (6H, m), 1.36−1.24 (13H, m). Anal. ($C_{32}H_{41}N_5O_4$·0.3H_2O) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-(2-ethoxy-ethylamino)-phenyl)-acetamide (32). Compound **32** was prepared by the same method used in the preparation of **6** except that **21** and **22f** were used in place of **19a** and **22a**, respectively, in step A (64%). ^{1}H NMR ($CDCl_3$) 8.45 (1H, s), 7.61 (1H, s), 7.56−7.47 (2H, m), 7.36 (4H, m), 7.03 (1H, d), 4.70 (2H, dd), 4.26 (2H, dd), 3.73 (2H, br s), 3.51 (4H, m), 2.82 (1H, br s), 2.05−1.65 (6H, m), 1.30−1.17 (16H, m). Anal. ($C_{32}H_{43}N_5O_4$·HCl) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-(methyl-(2-methylamino-ethyl)-amino)-phenyl)-acetamide (33). Compound **33** was prepared by the same method used in the preparation of **6** except that **21** and **22g** were used in place of **19a** and **22a**, respectively, in step A (19%). ^{1}H NMR ($CDCl_3$) 8.09 (1H, s), 7.50−7.45 (2H, m), 7.29−7.24 (1H, m), 7.12−7.01 (3H, m), 6.53−6.46 (2H, m), 4.69−4.67 (2H, m), 4.38 (1H, d, J = 13.8 Hz), 4.17 (1H, d, J = 13.8 Hz), 3.50−3.44 (2H, m), 2.93 (3H, s), 2.86−2.74 (3H, m), 2.49 (3H, s), 2.04−1.58 (7H, m), 1.31−1.19 (13H, m). Anal. ($C_{32}H_{44}N_6O_3$·0.5CH_2Cl_2) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-(1*H*-imidazol-1-yl)-phenyl)-acetamide (34). Compound **34** was prepared using step A of the method of preparation of **6** except that **21** and 3-imidazol-1-yl-phenylamine (**22h**)[31] were used in place of **19a** and **22a**, respectively (71%). ^{1}H NMR ($CDCl_3$) 8.57 (1H, s), 7.86 (1H, s), 7.71 (1H, t, J = 1.8 Hz), 7.52−7.28 (6H, m), 7.19 (1H, s), 7.11−7.08 (1H, m), 7.04−7.01 (1H, m), 4.84 (1H, d, J = 17.7 Hz), 4.58 (1H, d, J = 17.7 Hz), 4.24−4.23 (2H, m), 2.83−2.77 (1H, m), 2.05−1.67 (6H, m), 1.38−1.19 (13H, m). Anal. ($C_{31}H_{36}N_6O_3$·0.5H_2O) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-*m*-tolyl-acetamide (35). Compound **35** was prepared using step A of the method of preparation of **6** except that **21** and *m*-toluidine (**22i**) were used in place of **19a** and **22a**, respectively (79%). ^{1}H NMR ($CDCl_3$) 8.19 (1H, s), 7.48 (2H, m), 7.46 (2H, m), 7.28 (2H, m), 7.15 (1H, d), 6.87 (1H, m), 4.72 (1H, d), 4.65 (1H, d), 4.28 (1H, d), 4.20 (1H, d), 2.80 (1H, m), 2.30 (3H, s), 1.76−1.70 (6H, m), 1.29−1.19 (13H, m). Anal. ($C_{29}H_{36}N_4O_3$·0.5H_2O) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-methoxy-phenyl)-acetamide (36). Compound **36** was prepared using step A of the method of preparation of **6** except that **21** and *m*-anisidine (**22j**) were used in place of **19a** and **22a**, respectively (79%). ^{1}H NMR ($CDCl_3$) 8.22 (1H, m), 7.45−7.30 (2H, m), 7.27 (1H, m), 7.20−7.12 (2H, m), 7.03 (1H, d), 6.84 (1H, d), 6.63 (1H, d), 4.73 (1H, d), 4.64 (1H, d), 4.28 (1H, d), 4.19 (1H, d), 3.79 (3H, s), 2.80 (1H, m), 1.76−1.55 (6H, m), 1.36−1.24 (13H, m). Anal. ($C_{29}H_{36}N_4O_4$·0.5H_2O) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-hydroxy-phenyl)-acetamide (37). Compound **37** was prepared using step A of the method of preparation of **6** except that **21** and 3-aminophenol (**22k**) were used in place of **19a** and **22a**, respectively (35%). ^{1}H NMR ($CDCl_3$) 8.31 (1H, s), 7.68 (1H, s), 7.30 (2H, m), 7.26 (1H, m), 7.08 (2H, m), 6.60 (1H, m), 6.57 (1H, m), 6.41 (1H, m), 4.72 (1H, d), 4.65 (1H, d), 4.32 (1H, d), 4.22 (1H, d), 2.77 (1H, m), 1.98−1.69 (6H, m), 1.27−1.24 (13H, m). Anal. ($C_{28}H_{34}N_4O_4$·0.4H_2O) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-hydroxymethyl-phenyl)-acetamide (38). Step A. (3-(2-(5-Cyclohexyl-1,2-dihydro-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)acetamido)phenyl)methyl methyl carbonate was prepared using step A of the method of preparation of **6** except that **21** and **22l** were used in place of **19a** and **22a**, respectively (96%). ^{1}H NMR ($CDCl_3$) 8.30 (1H, s), 7.51−7.39 (4H, m), 7.31−7.24 (2H, m), 5.11 (2H, s), 4.72 (1H, d), 4.64 (1H, d), 4.23 (1H, d), 4.14 (1H, d), 3.80 (3H, s), 2.89 (1H, m), 1.76−1.67 (6H, m), 1.29−1.24 (13H, m).

Step B. (3-(2-(5-Cyclohexyl-1,2-dihydro-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)acetamido)-phenyl)methyl methyl carbonate was dissolved in THF−MeOH (1:1/40 mL), and 1% K_2CO_3 solution (30 mL) was added. The mixture was stirred at ambient temperature for 2 h. Following evaporation of the organic solvents, a precipitate formed which was isolated by filtration and dried in vacuo to afford **38** as a yellow solid (790 mg, 89%). ^{1}H NMR ($CDCl_3$) 8.31 (1H, s), 7.51−7.45 (3H, m), 7.31−7.28 (3H, m), 7.26−7.10 (2H, m), 4.70 (1H, d), 4.67 (2H, s), 4.64 (1H, d), 4.26 (1H, d), 4.22 (1H, d), 2.89 (1H, m), 1.85−1.55 (6H, m), 1.30−1.24 (13H, m). Anal. ($C_{29}H_{36}N_4O_4$·0.5H_2O) C, H, N.

3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (39). Step A. 3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic acid methyl ester was prepared using step A of the method of preparation of **6** except that **21** and 3-amino-benzoic acid methyl ester (**27m**) were used in place of **19a** and **22a**, respectively (71%). ^{1}H NMR ($CDCl_3$) 8.49 (1H, s), 7.92 (1H, m), 7.84 (1H, t), 7.74 (1H, dt), 7.48 (2H, m), 7.39−7.27 (2H, m), 7.03 (1H, d), 4.77 (1H, d), 4.60 (1H, d), 4.25 (2H, s), 3.91 (3H, s), 2.80 (1H, m), 2.05−1.73 (6H, m), 1.34−1.17 (13H, m).

Step B. Lithium hydroxide monohydrate (318 mg, 7.58 mmol) was added to a solution of 3-(2-(5-cyclohexyl-1-(3,3-dimethyl-2-

oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetyl-amino)-benzoic acid methyl ester (1.33 g, 2.49 mmol) in THF−H_2O (2:1/45 mL), and the mixture was stirred at ambient temperature for 16 h. The THF was evaporated under reduced pressure, and the aqueous solution was diluted with H_2O (50 mL) and acidified to pH 3 with 1 N HCl. The mixture was extracted with DCM (30 mL × 2), and the combined extracts were washed with brine (50 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent afforded **39** as an off-white solid (1.28 g, 99%). ^{1}H NMR (DMSO-d_6) 12.89 (1H, br s), 9.99 (1H, s), 8.16 (1H, s), 7.70 (1H, dd), 7.60−7.36 (4H, m), 7.26−7.15 (2H, m), 4.78 (2H, d), 4.30 (1H, d), 3.98 (1H, d), 2.87 (1H, m), 1.80−1.50 (6H, m), 1.34−1.13 (13H, m). The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{29}H_{34}N_4O_5 \cdot C_7H_{17}NO_5$) C, H, N.

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Supporting Information Available: Biological testing methods, elemental analysis of the novel compounds described in Table 2, and the X-ray crystallographic data for **19a** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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