5-Phenyl-3-ureidobenzazepin-2-ones as Cholecystokinin-B Receptor Antagonists

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A series of 5-phenyl-3-ureidobenzazepin-2-one cholecystokinin-B (CCK-B) receptor antagonists was synthesized using Beckmann ring expansion of a suitable 4-phenyl-1-tetralone as a key step. Structure–activity relationship studies revealed the importance of the 5-phenyl group for potent and selective CCK-B affinity. Addition of an 8-methyl substituent and resolution provided the potent (CCK-B IC_{50} = 0.48 nM) CCK-B antagonist **4**. The role of the 5-phenyl group as part of a "privileged structure" for high-affinity receptor antagonism is discussed.

Introduction

Cholecystokinin (CCK), a 33-amino acid polypeptide hormone discovered in 1929 on the basis of its control of gallbladder function,[1] mediates its effects through two receptors, termed CCK-A and CCK-B. Cloning and sequencing of these receptors, the CCK-A from rat[2] and human[3] and the CCK-B from human brain,[4] and the discovery of potent, selective antagonists for each receptor[5] have enabled characterization of their pharmacology. While the CCK-A receptor mediates primarily CCK's control of gallbladder function and digestive enzyme secretion, the CCK-B receptor is responsible for gastrin-stimulated acid secretion in the stomach during feeding[6,7] and for the panic behavior induced by CCK-4,[8] the C-terminal tetrapeptide fragment of CCK, a selective CCK-B agonist. The latter observation recommended the CCK-B receptor as a particularly intriguing therapeutic target, especially in light of the possible connection between panic disorder and anxiety.[9] In addition, the CCK-B receptor has been suggested to play a role in pain[10] and control of central dopaminergic function.[11]

CCK-B antagonists have been developed from numerous structural classes.[12] One of the most thoroughly investigated is the benzodiazepine family, represented by the potent and selective CCK-B antagonist L-365,260, 1, Figure 1.[13] Modification of the benzodiazepine nucleus of **1** to a 3-ureidobenzazepin-2-one was reported to afford relatively less potent and nonselective CCK antagonism.[14] For example, compound **2** (Figure 1) affords IC_{50} values of 140 and 110 nM at the CCK-A and CCK-B receptors, respectively. Incorporation of a phenyl group at the 5-position of the benzazepin-2-one nucleus, analogous to the pendant phenyl ring in **1**, was attempted in order to restore CCK-B affinity and selectivity (Figure 1). The structure–activity relationships (SAR) in a series of 5-aryl-3-ureidobenzazepin-2-ones which resulted in the discovery of the potent, selective CCK-B receptor antagonist CP-212,454, **4**, are reported herein.

Chemistry

The synthesis of the initial target structure **9** began with the known 5-phenylbenzazepin-2-one[15] as shown in Scheme 1. The elaboration of the side chains at N-1 and C-3 is based on a procedure originally developed for a series of angiotensin-converting enzyme inhibitors involving bromination, alkylation at N-1, azide displacement and reduction, and acylation with the requisite isocyanate.[16] An important issue in this series is the stereochemical relationship between the 5-phenyl group and the 3-ureido side chain because of its effect on biological activity. Since ^{1}H-NMR data could not establish this relationship unambiguously, X-ray determination of single-crystal samples of key intermediates was employed. Figure 2 shows single-crystal X-ray structures (depicted with Nemesis, Oxford Molecular Ltd.) for these three compounds. The first one is compound **5**, the major bromination product of 5-phenylbenzazepin-2-one, which is the *cis* diastereomer by X-ray analysis. This result, obtained in the other series as well as shown by correlation using ^{1}H-NMR data, can be rationalized as the result of axial attack by the incoming bromine on the intermediate imino chloride during the bromination, since the X-ray structure shows the new bromine in the axial conformation.

The X-ray structure of the succeeding compound in Figure 2 indicates that the subsequent reaction affords the *trans* isomer: the N-1 alkylation of the *cis* bromide **34** with *tert*-butyl iodoacetamide affords the *trans* product **35t**. This unexpected result can be rationalized by the ease of epimerization at the C-3 position under the strongly basic conditions of the alkylation and the greater thermodynamic stability of the *trans* product. Azide displacement afforded the expected *cis* relationship between C-3 and C-5 *via* S_N2 displacement, as indicated by the third X-ray structure in Figure 2, which depicts the major isomer of the product following azide displacement, reduction, and acylation, **43d**, in the 8-methyl series (Scheme 4). It is worthwhile noting that during the azide displacement reaction, the *trans* diastereomer was formed in increasing amounts, indicating it is the thermodynamically favored product, as is the case with the *trans* bromide precursor. To confirm these assignments and provide the *trans* isomer of the final product for comparison of biological activity, the azide displacement, reduction, and acylation were carried out on the *cis* bromide isomer in the 5-cyclohexyl series (Scheme 5), affording compound **58t**, which proved to have much lower affinity for the CCK-B receptor than the corresponding *cis* isomer **58c**. These data were then used to assign the stereochemistry of the other series, based on correlation with the X-ray structures and ^{1}H-

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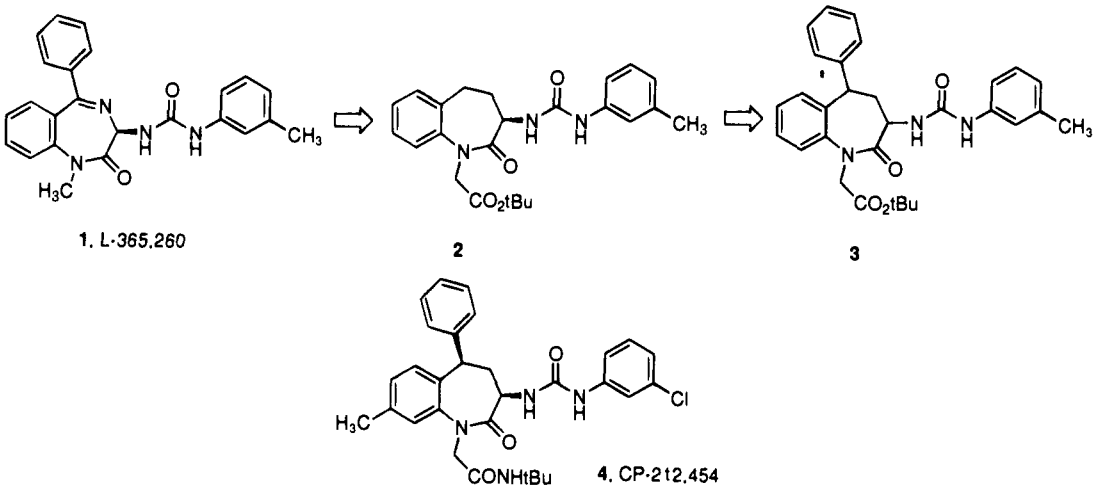
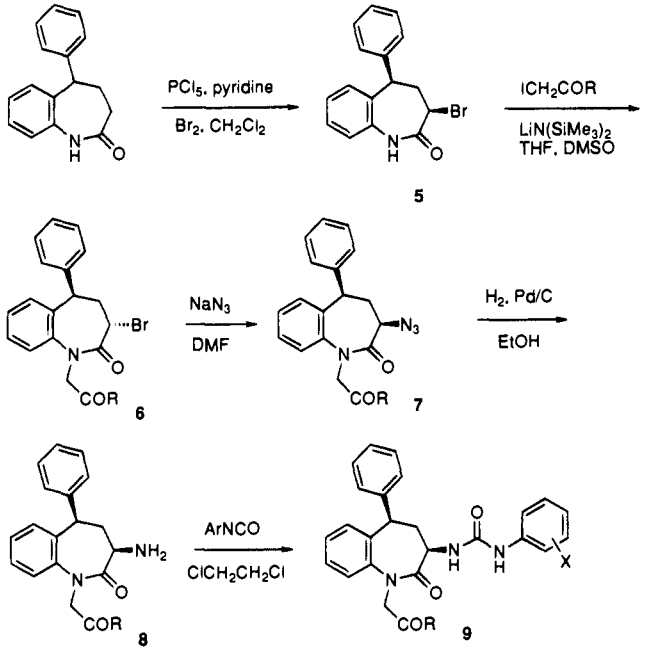


Figure 1. Development of 5-phenylbenzazepinon-2-one CCK-B antagonists.

Scheme 1. Preparation of 5-Phenylbenzazepin-2-one Compounds, Indicating the Major Diastereomer Obtained in Each Case[a]



6-9a, R = OtBu, X=CH_3
6-9b, R = NHtBu, X=CH_3
6-9c, R = N(CH_3)tBu, X=Cl
6-9d, R = NH(1,1-diMe)Et, X=Cl
6-9e, R = NH(1-Me)cyclohexyl, X=Cl
6-9f, R = NH(1,1-diMe)benzyl, X=Cl
9g, X = 3-OCH_3, R=NHtBu
9h, X = 3-Cl, R=NHtBu
9i, X = 4-Cl, R=NHtBu
9j, X = 2-CH_3, R=NHtBu
9k, X = 4-CH_3, R=NHtBu

[a] Absolute stereochemistry is depicted arbitrarily.

NMR data, with the position and $\Delta\nu$ value of the AB quartet pattern in the ^{1}H-NMR spectrum for the methylene next to the *tert*-butyl amide being diagnostic.

While the initial route provided compounds for SAR studies at the N-1 and C-3 positions, new routes were developed for generating SAR at the 5-, 7-, 8-, and 9-positions. The method shown in Scheme 2 for 7-substituted analogs begins with Stobbe condensation of diethyl succinate and the requisite benzophenone derivative.[17] After hydrolysis and hydrogenation, the resulting butyric acid derivative was cyclized to the tetralone by formation of the acid chloride and treatment with aluminum chloride. Only the expected tetralone **13a** was obtained from the acid **12a**; **13a** was converted to the final product **22a** by oxime formation and Beckman rearrangement with polyphosphoric acid, followed by the chemistry employed in Scheme 1. In the case of the 3-chlorophenyl analog **12b**, cyclization provided a mixture of the 6-chloro-4-phenyltetralone **13b** and the 4-(3-chlorophenyl)tetralone **14**, which was converted to the mixed oximes. The 4-(3-chlorophenyl) isomer **16b** crystallized while the 6-chloro-4-phenyl isomer **15b** remained an oil, providing the basis for a separation of these two compounds. Each isomer was then carried to the final products, **22b** and **27**, respectively. The regiochemical assignment was based on comparison of ^{1}H-NMR data with the 7-methyl series, **13a**–**22a**.

Since the benzophenone route could not provide the 9-substituted benzazepin-2-one nucleus due to steric hindrance during the cyclization to the intermediate tetralone, a new route was investigated, as shown in Scheme 3. The known 8-methyl-1-naphthol[18] was subjected to aluminum chloride-catalyzed condensation with benzene as reported for naphthol,[19] but two tetralone products, apparently isomeric, were obtained. Crystallization and X-ray analysis showed that in addition to the expected 8-methyl-4-phenyl-1-tetralone, **28**, a greater amount of 7-methyl-4-phenyl-1-tetralone, **29a**, was also obtained. The details of this curious rearrangement are still unclear, though **28** does not form **29a** when resubjected to the reaction conditions. This suggests the rearrangement to the thermodynamically favored, less sterically crowded **29a** occurs through a reaction intermediate, possibly a cationic intermediate formed upon condensation of the 8-methyl-1-naphthol with benzene, which rearranges to place the cation at the 7-position of the bicyclic nucleus, allowing 1,2 (1,5) methyl migration and aromatization to **29a**. In the event, both **28** and **29a** were converted to final products **38** and **43a** by using the chemistry described in Scheme 1.

Once the need for further 8-substituted analogs had been established by the improved *in vitro* activity of the 8-methyl compound **43a**, a more general route to the intermediate 7-substituted 1-naphthol derivatives was developed as shown in Scheme 4. The key step in the route relies on the aromatization of an appropriately substituted tetralone derivative, using DDQ oxidation of the enol acetate.[20] One further reaction deserves comment: the Beckmann rearrangement of **31** to **33**. After considerable experimentation with alternative

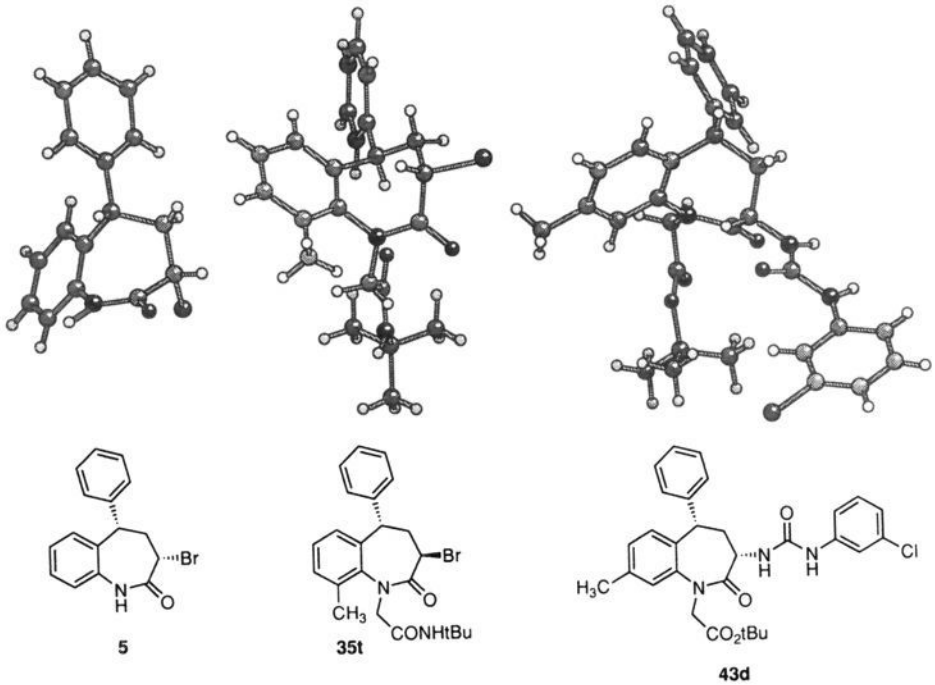


Figure 2. Structures of three key intermediates in the 5-phenylbenzazepin-2-one synthesis demonstrating the stereochemical outcome. Absolute stereochemistry is arbitrarily depicted.

conditions,[21] it was found that polyphosphoric acid ethyl ester (PPE)[22] gave a clean, high-yield conversion. The remaining chemistry follows previous schemes, furnishing, in addition to the 8-methyl compounds **43a** and **43d**, the 8-ethyl-5-phenylbenzazepin-2-one analog **43b** and the 8-chloro-5-phenylbenzazepin-2-one analog **43c**.

Scheme 5 depicts the first route used to prepare the 5-cyclohexylbenzazepin-2-one derivative **58c** and its *trans* isomer **58t**. Thus commercially available[23] 1-cyclohexylphenylacetic acid was converted to the alcohol, tosylate, and iodide and homologated with diethyl malonate, to afford, following hydrolysis and decarboxylation, 4-cyclohexyl-4-phenylbutyric acid (**50**). The remainder of the synthesis followed previous chemistry to afford **58c** and **58t**. To incorporate the 8-methyl substituent into this nucleus for analog **68a**, the route shown in Scheme 4 was modified by adding the cyclohexyl group as the Grignard reagent to methyl 3-toluoylpropionate, as shown in Scheme 6. Reduction of the lactone **59** was carried out with triethylsilane in trifluoroacetic acid to afford the requisite butyric acid **60** for the remainder of the synthesis as before. This route was subsequently used for the other 5-substituted analogs **68b** and **68c**. Finally, Scheme 7 depicts the route to the 5-(4-tolyl)benzazepin-2-one analog **78**, which uses the method shown in Scheme 2.

The preparation of **4** and **82**, the enantiomers of **43a**, was achieved by separation of diastereomers **80a** and **80b** prepared by derivatization of **42a** with *t*-BOC-L-phenylalanine and deprotection[24] as shown in Scheme 8. Edman degradation removed the chiral auxiliary and acylation with 3-chlorophenyl isocyanate provided **4** and **82**.

Biology

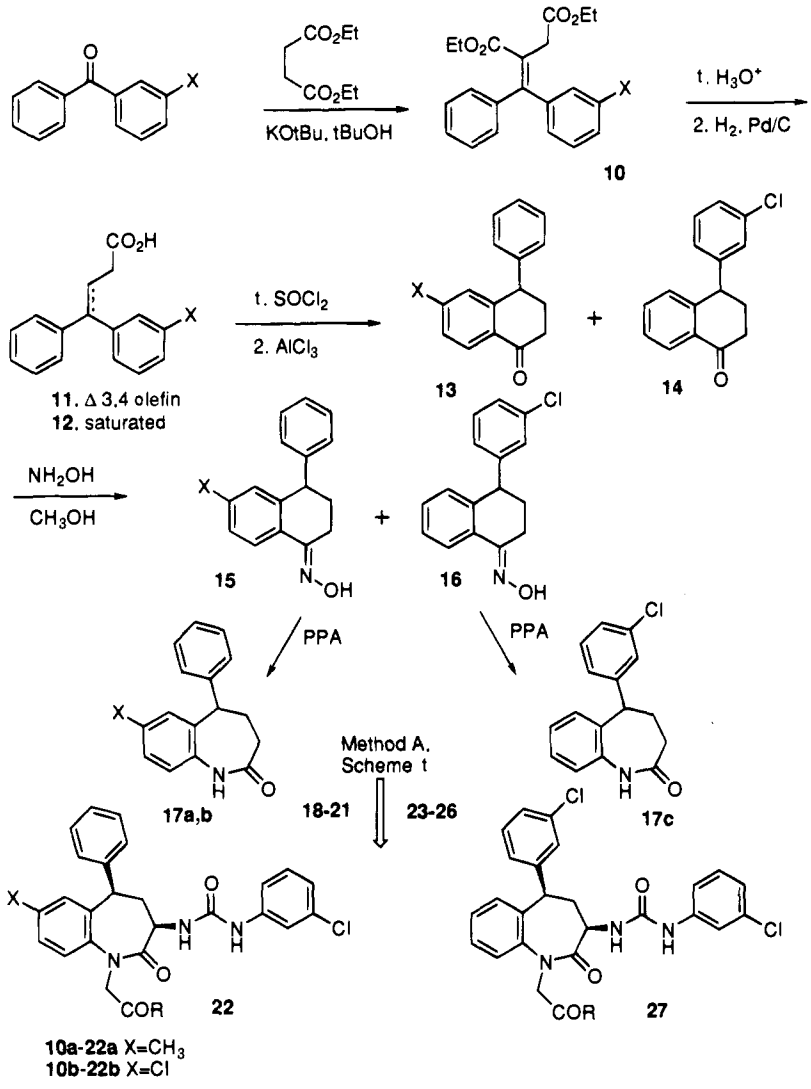
In vitro receptor binding assays were used to measure affinities at the CCK-B and CCK-A receptors. Briefly, the displacement of [^{125}I]BH-CCK-8 was measured for test compounds in a guinea pig cortex preparation for CCK-B receptors and in guinea pig pancreas for CCK-A receptors. *In vivo* efficacy was measured in anaesthetized rats by assaying stomach acid 2 h following administration of pentagastrin in the presence of a test compound.

Results and Discussion

The initially selected target, 5-phenyl-3-ureidobenzazepin-2-one **9a**, shows potent affinity for the CCK-B receptor in guinea pig cortex and moderate selectivity over the CCK-A receptor in guinea pig pancreas (Table 1). This result validates the hypothesis that incorporation of the 5-substituent to mimic the pendant phenyl ring in L-365,260 is important for achieving potent CCK-B affinity, as seen by comparison with the data cited above for compound **3**. Concerns over the metabolic stability of the ester group in **9a** prompted synthesis of the *tert*-butyl amide analog **9b**, which also shows potent and selective CCK-B receptor affinity (Table 1). Other amides tested illustrate the decrease in selectivity for monosubstituted compounds (**9c**) and increased CCK-B affinity for smaller amides (**9d** and **9f**). The 1-methylcyclohexyl amide **9e** improves selectivity for the CCK-B receptor without sacrificing potent affinity. Table 1 also shows the effect of substitution on the ureido side chain phenyl ring, with the 3-chloro (**9h**) substituent affording the best balance of potent affinity and selectivity for the CCK-B receptor. Thus **9h** was selected for further modification.

The effect of substitution on the benzazepin-2-one nucleus was next examined, with the 7-substituted **22a** and **22b** affording lower CCK-B affinity, while 8- and 9-substituents increased CCK-B affinity (Table 2). The improved CCK-B affinity of **38** comes with a decrease of selectivity, while the most potent compound in this series, **43a**, has improved CCK-B selectivity as well. In addition, **43a** is more potent and selective than the

Scheme 2. Preparation of 7-Substituted, 5-Phenylbenzazepin-2-one and 5-(3-Chlorophenyl)benzazepin-2-one Compounds



corresponding 8-ethyl and 8-chloro compounds **43b** and **43c** and the corresponding ester analog **43d**. Resolution of **43a** provided **4** and **82**, with most of the desired affinity at the CCK-B receptor residing in the (+) enantiomer **4**.

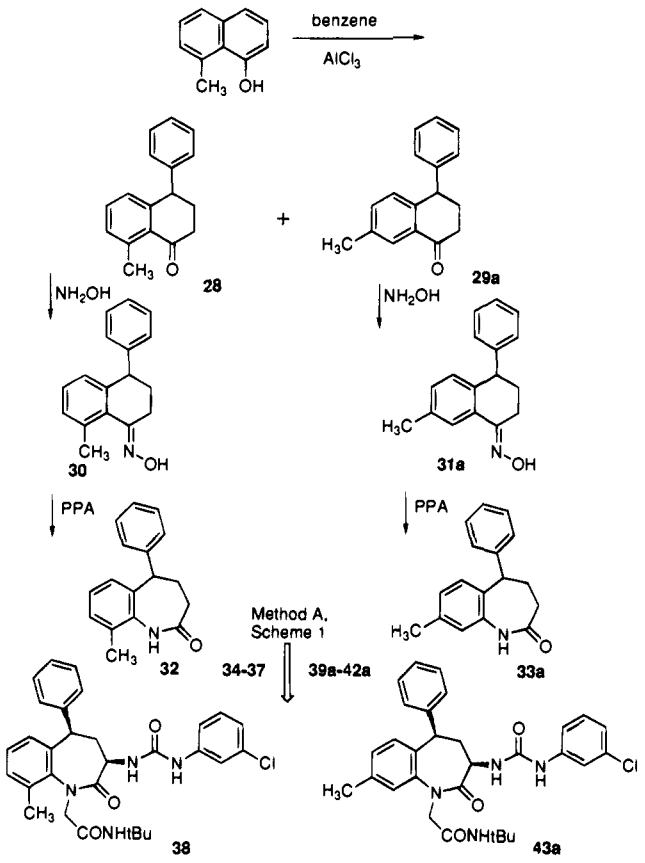
Variation of the 5-substituent further confirmed the important role it plays in this series of compounds (Table 3). The approximately 100-fold loss of CCK-B receptor affinity for the *trans* relative to the *cis* isomer in this series of compounds as illustrated with **58c** and **58t** indicates that the stereochemistry at the 5-position is important for CCK-B receptor affinity. While decreasing the steric size of the 5-substituent to an isopropyl group in **68c** decreases CCK-B selectivity, extending it to a benzyl group in **68b** dramatically increases selectivity. Addition of a single methyl group in the para position of the 5-phenyl ring, as in **78**, also increases CCK-B selectivity by decreasing affinity for the CCK-A receptor, illustrating the sensitivity of the CCK-A receptor to substitution in this region of the benzazepin-2-one structure. Substitution at other positions of the 5-phenyl ring had little effect on receptor affinity, as illustrated by compound **27**. The 5-cyclohexyl compound **68a** provided potent CCK-B receptor affinity and selectivity.

Consistent with its potent CCK-B receptor blockade *in vitro*, **4** potently inhibited pentagastrin-induced acid secretion in the guinea pig, with an ED_{50} value of 0.80 mg/kg sc, compared with a value of 1.5 mg/kg sc for compound **1**.

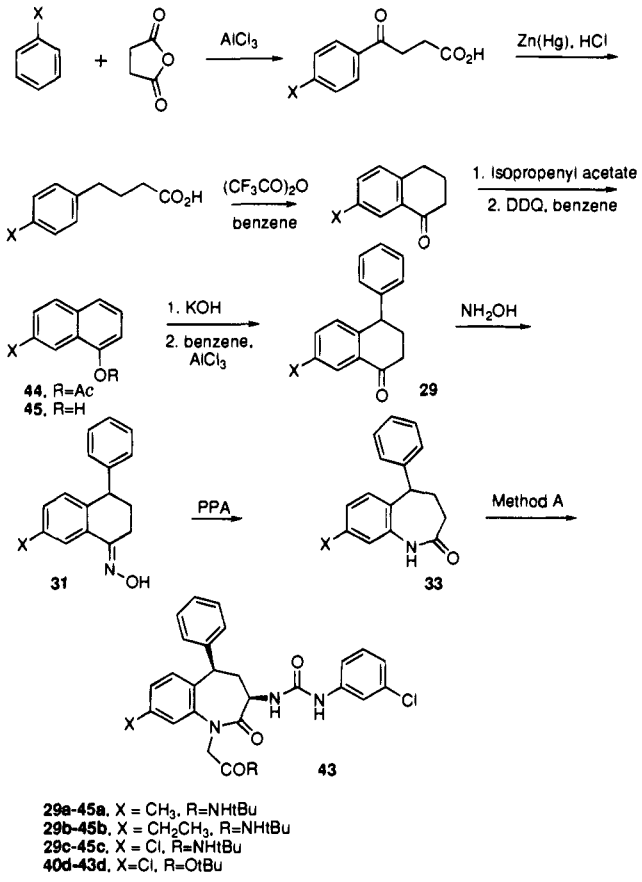
Conclusion

Incorporation of a 5-phenyl ring into a series of 3-ureidobenzazepin-2-one structures affords compounds with potent and selective affinity for the CCK-B receptor. This 5-phenylbenzazepin-2-one structure thus provides a new "template" for receptor antagonists, joining the collection of "privileged structures" chemists use in antagonist design.[25] The receptor binding site for one such "privileged structure", the benzhydryl group of the substance P (SP) antagonist CP-96,345, has been located to a histidine residue, numbered 197, in the fifth helical transmembrane domain of the NK-1 receptor for SP.[26] A key residue, valine 319, in the adjoining sixth transmembrane domain of the cholecystokinin receptor has been identified as important for recognition of the benzodiazepine ligand **1**.[27] Since the NK-1, CCK-A, and CCK-B receptors all belong to the G protein-coupled receptor superfamily of proteins, the antagonist binding site on these receptors may be a conserved structural

Scheme 3. Preparation of 8- and 9-Substituted, 5-Phenylbenzazepin-2-one Compounds



Scheme 4. Preparation of 8-Substituted, 5-Phenylbenzazepin-2-ones



feature, much as the "double-ring motif" is a conserved structural feature of the antagonists.[28] Hence by expanding the library of "privileged structures" and their SAR, chemists may provide a tool for understanding the mechanism of receptor antagonism while at the same time enabling more efficient discovery of antagonists at new receptors.

Experimental Section

Melting points were obtained on a Hoover melting point apparatus and are uncorrected. NMR spectra were obtained on a Varian XL-300 or a Bruker AM-300 spectrometer, with trimethylsilane as internal standard. IR spectra were obtained on Perkin-Elmer 283B and 1420 spectrometers. Mass spectra were obtained on a Finnegan 4510 mass spectrometer, and high-resolution mass spectra were obtained on an AE-9 instrument. Tlc analysis was carried out on EM Kieselgel 60 F_{254} 5 × 20 cm plates. Elemental analyses were carried out by the Analytical Laboratory of Pfizer Central Research and are within ±0.4% of theory unless otherwise noted. Physical properties of final products are listed in Table 4. The following compounds were prepared by literature methods: 5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one,[16] 1-methylcyclohexylamine,[29] 8-methyl-1-naphthol,[30] 7-methyl-1,2,3,4-tetrahydronaphth-1-one,[31] 7-ethyl-1,2,3,4-tetrahydronaphth-1-one,[32] 7-chloro-1,2,3,4-tetrahydronaphth-1-one,[33] 4-benzyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one, **61b**,[34] and 4-isopropyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one, **61c**.[35]

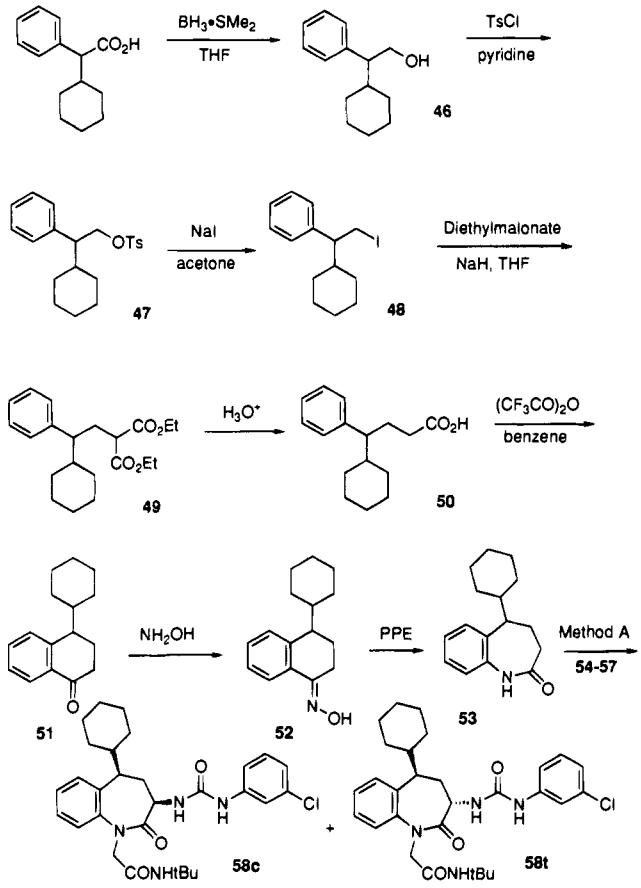
Method A. Preparation of *tert*-Butyl 2-[3-(3-(3-Tolyl)-ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoate, (9a): 3-Bromo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (5). To a 125 mL round-bottomed flask containing 1.041 g (5 mmol) of PCl_5 dissolved in 50 mL of methylene chloride under nitrogen in an ice/acetone bath was added 1.187 g (5 mmol) of 5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. A slight temperature rise was noted, and then 0.42 mL (5.25 mmol) of pyridine in 5 mL of methylene chloride was added rapidly dropwise. The mixture was stirred for 15 min and then cooled to −45 °C. Then 0.258 mL (5 mmol) of bromine in 7 mL of methylene chloride was added dropwise over 30 min with rapid stirring. The bath was removed after 15 min, and the mixture was allowed to come to room temperature. Thin-layer chromatography (TLC) (silica gel, 23:2, methylene chloride:ethyl acetate) showed no starting material, only a nonpolar intermediate (imino chloride). The remainder of the reaction was diluted with an equal volume of tetrahydrofuran, and 200 mL of water added. This mixture was stirred for 40 min and then separated. The aqueous layer was re-extracted with methylene chloride, and the combined organic fractions were washed with water, dried with brine and sodium sulfate, filtered, and evaporated, yielding 1.56 g (98.7%) of crude product.

The diastereomeric bromides (R_f = 0.57, and 0.48) may be separated by chromatography or crystallized from ether and hexane; however, the mixture was used directly in the next step.

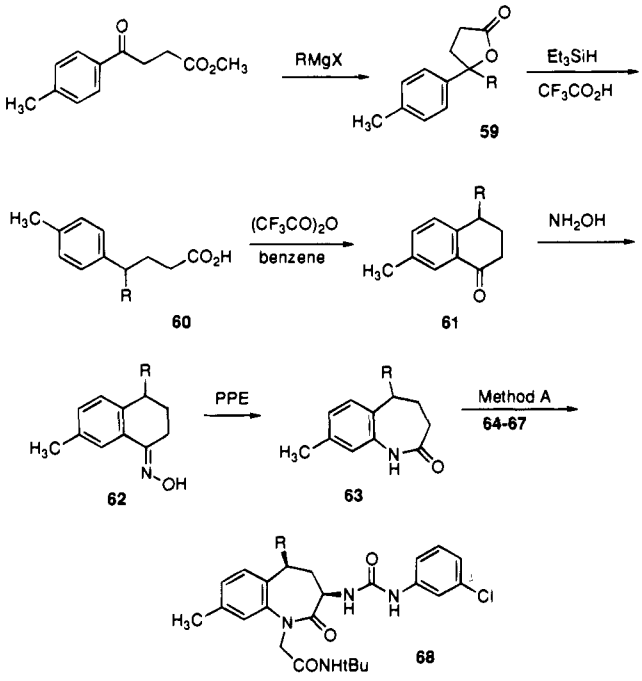
The solid obtained by crystallization was predominantly the more polar isomer while the mother liquor contained more of the less polar isomer as well as traces of the imino chloride and starting material. Recrystallization of the more polar diastereomer from chloroform gave large crystals: mp 191–192 °C; ^{1}H-NMR (δ, $CDCl_3$) 2.92 (m, 1H), 3.14 (m, 1H), 4.49 (m, 1H), 4.63 (m, 1H), 6.77 (d, 1H), 7.09 (m, 3H), 7.32 (m, 6H), 7.85 (bs, 1H); MS (%) 315/317 (parent for Br^{79}/Br^{81}, 20/18), 236 (78), 208 (100), 194 (36), 180 (73), 130 (47), 115 (39), 91 (79).

Single-Crystal X-ray Analysis of 5. A representative crystal was surveyed and a 1 Å data set (maximum sin Θ/λ = 0.5) was collected on a Nicolet R3m/μ diffractometer. Atomic scattering factors were taken from ref 36. All crystallographic calculations were facilitated by the SHELXTL[37] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table A1 (supplementary material). A trial structure was obtained by direct methods. This trial structure was refined routinely. A difference map revealed a chloroform

Scheme 5. Preparation of *cis*-5-Cyclohexylbenzazepin-2-one **58c** and *Trans* Isomer **58t**



Scheme 6. Preparation of 5-Substituted 8-Methylbenzazepin-2-one Analogs **68**



59-68a, R = cyclohexyl
59-68b, R = benzyl
59-68c, R = 2-propyl

of crystallization that was disordered around the 2-fold axis. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogen on nitrogen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R index was 9.78%. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELX-TL plotting package and redrawn for Figure 2 using the Nemesis (Oxford Molecular, Ltd.) program. Coordinates, anisotropic temperature factors, distances, and angles are available as supplementary material (Tables A2–A6).

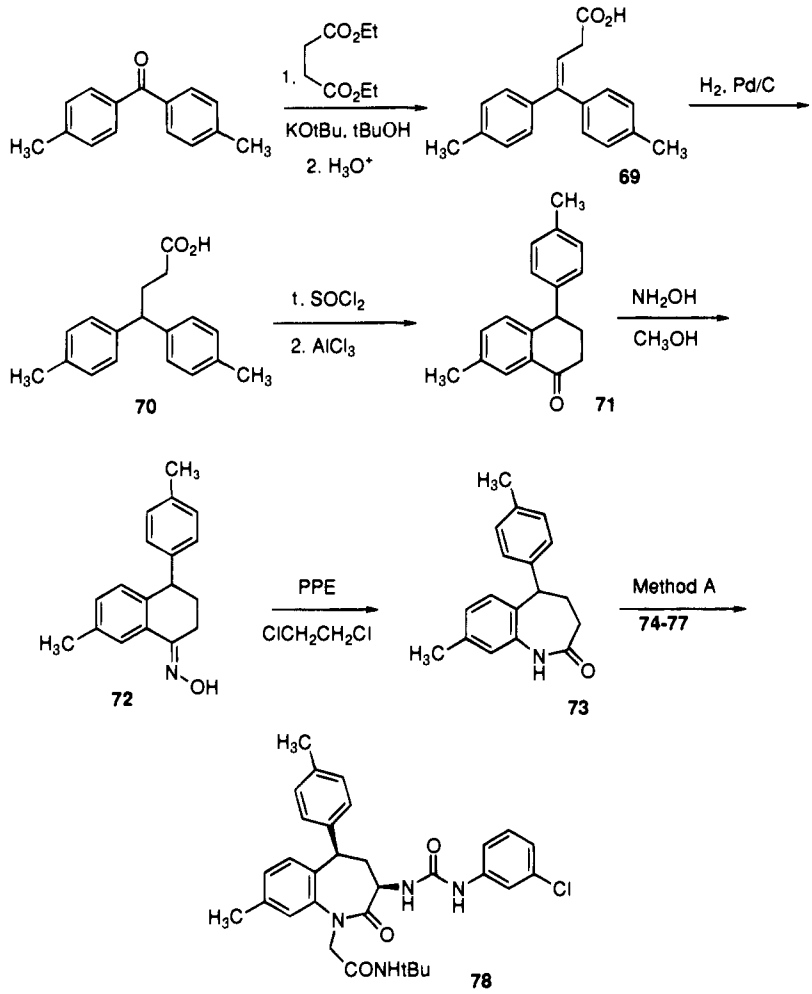
***tert*-Butyl 2-(3-Bromo-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoate (6).** To a 125 mL three-neck round bottomed flask equipped with septum and N_2 inlet were added 1.264 g (4.0 mmol) of **5** and 20 mL of dry tetrahydrofuran (THF) under nitrogen. The reaction mixture was cooled in a dry ice bath, and 4.4 mL of 1 M (in THF) lithium bis(trimethylsilyl) amide was added slowly. The mixture was stirred for 5 min. Then 1.065 g (4.4 mmol) of *tert*-butyl iodoacetate was added. The bath was removed, and 25 mL of dimethyl sulfoxide (DMSO) was added at −20 °C. After 1 h at room temperature, an acidified aliquot showed only a trace of starting material by TLC (24:1 CH_2Cl_2:EtOAc). The reaction mixture was poured into ice water and ethyl acetate containing 25 mL of 1 N hydrochloric acid, stirred for 5 min, and separated. The ethyl acetate extraction was repeated, and the combined extracts were washed three times with water, dried with brine and sodium sulfate, filtered, and evaporated, yielding 1.641 g (95%) of an oil: ^{1}H-NMR (δ, $CDCl_3$) 1.48 (s, 9H), 2.7–3.1 (m, 2H), 4.5–4.7 (m, 1H), 4.57 (AB q, J_{AB} = 17, $\Delta\nu$ = 99, 2H), 5.06 (m, 1H), 6.03 (d, J = 11, 1H), 7.0–7.4 (m, 8H).

***tert*-Butyl 2-(3-Azido-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoate (7).** To a 250 mL round-bottomed flask equipped with N_2 inlet were added 4.376 g (10.17 mmol) of **6**, 50 mL of dimethylformamide (DMF), and 2.626 g (40.4 mmol, under nitrogen) of sodium azide, and the mixture was heated at 70 °C for 14 h with stirring. The reaction mixture was then cooled, distributed between water and ethyl acetate, and separated, and the aqueous phase was again extracted. The combined extracts were washed with water three times and with bicarbonate solution once, then dried with brine and sodium sulfate, filtered, and evaporated, leaving a gummy residue, 4.53 g (>100%), containing some solvent: ^{1}H-NMR (δ, $CDCl_3$) 1.48 (s, 9H), 2.88 (m, 2H), 4.52 (AB q, J_{AB} = 17, $\Delta\nu$ = 138, 2H), 4.57 (m, 1H), 5.06 (m, 1H), 6.73 (d, 1H), 7.26 (m, 8H); IR (cm^{-1}, neat) 2082 (N_3), 1745, 1685 (C=O).

***tert*-Butyl 2-(3-Amino-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoate (8).** The crude product from the previous displacement reaction, 3.99 g (10.17 mmol) of **7**, was dissolved in 75 mL of methanol under nitrogen. The catalyst, 2 g of 5% Pd/C, was added, and the mixture was hydrogenated at 55 psi of H_2 for 5 h. The mixture was filtered through Celite, the catalyst washed three times with methanol, and the filtrate evaporated. TLC (24:1 methylene chloride:methanol, silica gel), showed less polar material and the product at R_f = 0.25. The crude product taken up in ethyl acetate and extracted with acid. The acidic extract was back-washed with ethyl acetate, and then the aqueous fraction was taken with fresh ethyl acetate and the pH adjusted to 10.0. The organic fraction was then dried with brine and sodium sulfate, filtered, and concentrated, yielding 885 mg (24%) of the crystalline amine, mp 189–192 °C: ^{1}H-NMR (δ, $CDCl_3$) 1.41 (s, 9H), 3.0–3.3 (m, 2H), 3.15 (AB q, J_{AB} = 17, $\Delta\nu$ = 120, 2H), 4.1 (m, 1H), 4.2 (m, 1H), 7.0–7.4 (m, 9H); IR (cm^{-1}, neat) 1745, 1690 (C=O); MS (rel int) 366 (parent, 20), 264 (90), 206 (100).

***tert*-Butyl 2-(3-(3-(3-Tolyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoate (9a).** To a 25 mL round-bottomed flask equipped with N_2 inlet were added 0.732 g (2 mmol) of **8** and 5 mL of methylene chloride under nitrogen, and the reaction was cooled in an ice bath. A solution of 0.283 mL (2.2 mmol) of *m*-tolyl isocyanate in 5 mL of methylene chloride was then added dropwise. Stirring was continued for 15 min, and then the ice bath was removed,

Scheme 7. Preparation of 8-Methyl-5-(4-tolyl)benzazepin-2-one **78**



allowing the reaction to come to room temperature for several hours. The reaction mixture was evaporated and the residue taken up in ethyl acetate, washed with dilute hydrochloric acid and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel, and the product fractions were triturated with hexane:ethyl acetate, 1:1, to afford a white solid: mp 191–192 °C; 300 mg (30%); ^{1}H-NMR (δ, $CDCl_3$) 1.4 (s, 9H), 2.29 (s, 3H), 2.72 (m, 1H), 3.19 (m, 1H), 3.28 (AB q, J_{AB} = 16, $\Delta\nu$ = 230, 2H), 4.22 (m, 1H), 4.7 (m, 1H), 6.37 (broad s, 1H), 6.78–7.5 (m, 14H); MS (rel int) 500 (18, parent + 1), 484 (4), 444 (20), 426 (4), 337 (42), 311 (100), 266 (20), 240 (30), 194 (34). Anal. ($C_{30}H_{33}N_3O_4$) C, H, N.

Method B. Preparation of *N-tert*-Butyliodoacetamide. *N-tert*-Butylchloroacetamide. To a 1 L round-bottomed flask equipped with N_2 inlet were added 15.08 mL (200 mmol) of chloroacetyl chloride and 400 mL of ethyl acetate. The solution was cooled to 10 °C, and a solution of 42 mL (400 mmol) of *tert*-butylamine in 75 mL of ethyl acetate was added dropwise over 20 min, and the solution stirred and allowed to come to room temperature overnight. The reaction mixture was filtered and the white precipitate washed twice with ethyl acetate. The combined filtrates were washed with water, dilute phosphoric acid solution, water, dilute sodium bicarbonate solution, and brine, dried over sodium sulfate, filtered, and evaporated to afford 26.2 g (87.5%) of an oil, which was used directly in the next step: ^{1}H-NMR (δ, $CDCl_3$) 1.39 (s, 9H), 3.96 (s, 2H), 6.3 (bs, 1H).

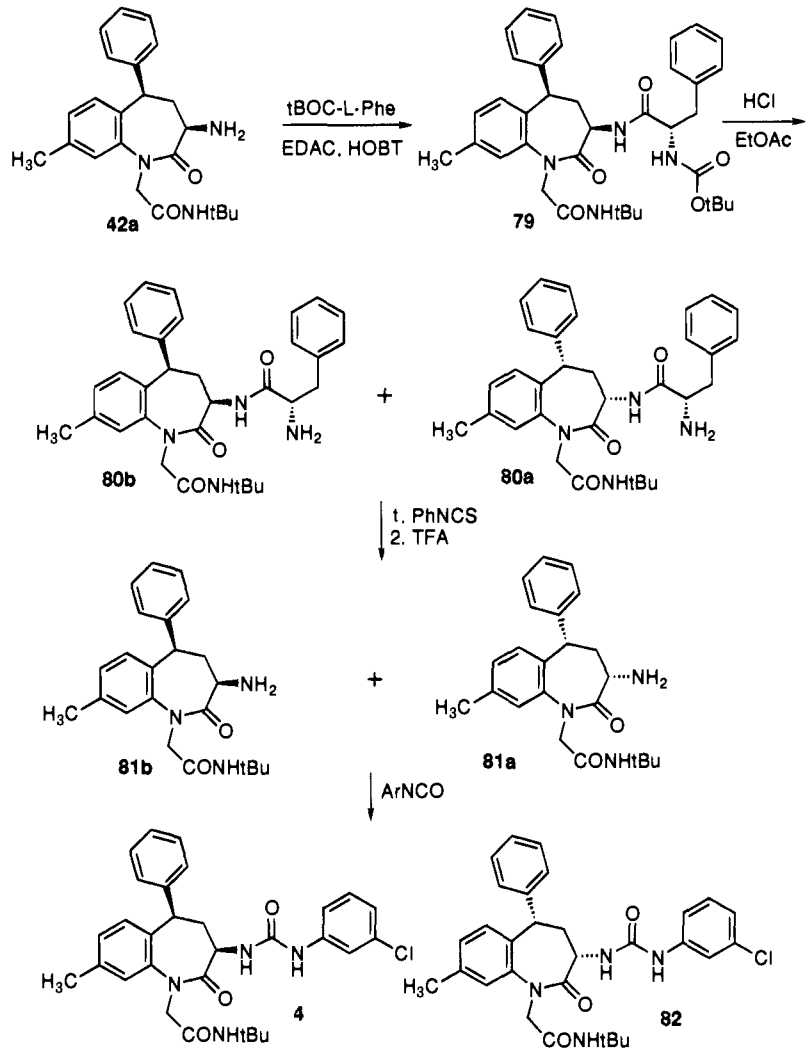
***N-tert*-Butyliodoacetamide.** To a 1 L round-bottomed flask equipped with N_2 inlet were added the above oil (26.2 g, 175 mmol) and 300 mL of dry acetone. A stream of dry nitrogen was bubbled through the solution for several minutes, followed by addition of 28.9 g (192.5 mmol) of sodium iodide. The nitrogen stream was continued for several minutes, and then the reaction mixture was refluxed for 3 h under a N_2 atmosphere. The reaction mixture was cooled and filtered, and the filtrate was evaporated. The residue was taken up in ethyl acetate, washed twice with water and once with brine, dried over sodium sulfate, filtered, and concentrated to a slurry. Hexane was added, and the slurry was filtered and washed with hexane:ethyl acetate, 2:1, to afford a white solid: 18.46 g (44%); mp 103.5–104 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.34 (s, 9H), 3.62 (s, 2H), 5.8 (bs, 1H).

Preparation of *N-tert*-Butyl-2-[3-(3-(3-tolyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]-ethanoic Acid Amide (9b): *N-tert*-Butyl-2-(3-bromo-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)-ethanoic acid amide (6b) was prepared according to method A using *N-tert*-butyliodoacetamide, mp 111.5–112.5 °C, in 87% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.41 (s, 9H), 2.92 (m, 1H), 3.07 (m, 1H), 4.42 (bs, 2H), 4.62 (dd, J = 6, 12, 1H), 4.70 (m, 1H), 6.07 (bs, 1H, *N*H), 6.73 (m, 1H), 7.12 (m, 1H), 7.2–7.4 (m, 7H); MS (rel int) 429/431 (parent + 1, Br^{79}/Br^{81}, 93/90), 356/358 (Br^{79}/Br^{81}, 100/98), 276/278 (Br^{79}/Br^{81}, 50/45), 248/250 (Br^{79}/Br^{81}, 60/52), 133 (72).

***N-tert*-Butyl-2-(3-azido-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (7b)** was prepared according to method A, mp 112–117 °C, in 74% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.48 (s, 9H), 2.88 (m, 2H), 4.52 (AB q, J_{AB} = 17, $\Delta\nu$ = 138, 2H), 4.57 (m, 1H), 5.06 (m, 1H), 6.73 (d, 1H), 7.26 (m, 8H); IR (cm^{-1}, Nujol) 2090 (N_3), 1675 (C=O); MS (rel int) 391 (parent, 90), 263 (60), 206 (100), 160 (80), 91 (85); HRMS calcd for $C_{22}H_{25}N_5O_2$ 391.2008, found 391.20014.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (8b)** was prepared according to method A in 72% yield, mp 196–196.5 °C. This material was obtained in two crops by crystallizing the reaction mixture from methanol. The remaining mother liquor contained predominantly the *trans* diastereomer, which

Scheme 8. Resolution of Benzazepin-2-ones To Produce Compounds **4** and **82**



was also used as indicated below: ^{1}H-NMR (δ, $CDCl_3$) 1.30 (s, 9H), 2.2 (bs, 2H), 3.06 (AB q, J_{AB} = 15, $\Delta\nu$ = 276, 2H), 2.67 (m, 1H), 2.84 (m, 1H), 3.57 (m, 1H), 4.18 (m, 1H), 6.01 (bs, 1H), 7.2 (m, 9H). Anal. ($C_{22}H_{27}N_3O_2 \cdot {}^1/_4H_2O$) C, H, N.

***N-tert*-Butyl-2-[3-(3-(3-tolyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (9b)** was prepared according to method A in 88% yield: mp 263–266 °C; ^{1}H-NMR (δ, DMSO-d_6) 1.23 (s, 9H), 2.21 (s, 3H), 2.54 (m, 1H), 2.9 (m, 1H), 3.34 (AB q, J_{AB} = 16, $\Delta\nu$ = 255, 2H), 3.4 (HOD peak), 4.34 (m, 2H), 6.8 (m, 2H), 7.3 (m, 11H), 8.78 (s, 1H); MS (rel int) 499 (parent + 1, 100), 426 (60), 293 (34), 194 (34); HRMS calcd for $C_{30}H_{35}N_4O_3$ (parent + 1) 499.2709, found 499.270 00. Anal. ($C_{30}H_{35}N_4O_3 \cdot {}^1/_2H_2O$) C, H, N.

***N-tert*-Butyl-2-[3-(3-(3-methoxyphenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (9g)** was prepared according to method A in 81% yield: mp 254–257 °C; ^{1}H-NMR (δ, DMSO-d_6) 1.21 (s, 9H), 2.56 (m, 1H), 2.9 (m, 1H), 3.33 (AB q, J_{AB} = 16, $\Delta\nu$ = 259, 2H), 4.35 (m, 2H), 6.4–7.6 (m, 14H), 8.865 (broad s, 1H); MS (rel int) 514 (0.1, parent), 322 (6), 149 (100), 106 (40); HRMS calcd for $C_{30}H_{34}N_4O_4$ 514.2553, found 514.261 34. Anal. ($C_{30}H_{34}N_4O_4 \cdot {}^1/_2H_2O$) C, H, N.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (9h)** was prepared according to method A in 90% yield: mp 264–266 °C; ^{1}H-NMR (δ, DMSO-d_6) 1.21 (s, 9H), 2.56 (m, 1H), 2.9 (m, 1H), 3.35 (AB q, J_{AB} = 17, $\Delta\nu$ = 255, 2H), 4.37 (m, 2H), 6.7–7.6 (m, 14H), 9.08 (s, 1H); MS (rel int) 518 (1, parent), 322 (40), 194 (60), 91 (70), 58 (100); HRMS calcd for $C_{29}H_{31}N_4O_3Cl$ 518.2097, found 518.2100. Anal. ($C_{29}H_{31}ClN_4O_3 \cdot {}^1/_5CH_2Cl_2$) C, H, N.

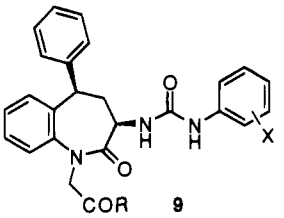
***N-tert*-Butyl-2-[3-(3-(4-chlorophenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (9i)** was prepared according to method A in 88% yield: mp 247–249 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.31 (s, 9H), 2.92 (m, 1H), 3.10 (m, 1H), 3.22 (AB q, J_{AB} = 16, $\Delta\nu$ = 260, 2H), 4.29 (m, 1H), 4.60 (m, 1H), 5.74 (broad s, 1H), 6.43 (broad s, 1H), 7.0–7.5 (m, 13H); MS (rel int) 518 (1, parent), 322 (40), 261 (70), 153 (100); HRMS calcd for $C_{29}H_{31}N_4O_3Cl$ 518.2070, found 518.210 07. Anal. ($C_{29}H_{31}N_4O_3Cl \cdot {}^1/_2CH_2Cl_2$) C, H, N.

***N-tert*-Butyl-2-[3-(3-(2-tolyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (9j)** was prepared according to method A in 85% yield: mp 231–233 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.28 (s, 9H), 2.24 (s, 3H), 2.65 (m, 1H), 3.09 (AB q, J_{AB} = 17, $\Delta\nu$ = 291, 2H), 3.11 (m, 1H), 4.22 (m, 1H), 4.62 (m, 1H), 6.01 (broad s, 1H), 6.41 (broad s, 1H), 6.9–7.5 (m, 13H); MS (rel int) 498 (0.5, parent), 322 (5), 249 (8), 133 (80), 105 (100), 78 (80); HRMS calcd for $C_{30}H_{34}N_4O_3$ 498.2630, found 498.254 75. Anal. ($C_{30}H_{34}N_4O_3 \cdot {}^1/_2H_2O$) C, H, N.

***N-tert*-Butyl-2-[3-(3-(4-tolyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (9k)** was prepared according to method A in 95% yield: mp 235–238 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.29 (s, 9H), 2.27 (s, 3H), 2.72 (m, 1H), 3.12 (m, 1H), 3.25 (AB q, J_{AB} = 16, $\Delta\nu$ = 283, 2H), 4.24 (m, 1H), 4.60 (m, 1H), 5.88 (broad s, 1H), 6.8–7.4 (m, 14H); MS (rel int) 498 (1, parent), 322 (30), 249 (15), 221 (20), 194 (20), 133 (100); HRMS calcd for $C_{30}H_{34}N_4O_3$ 498.2646, found 498.261 53. Anal. ($C_{30}H_{34}N_4O_3 \cdot {}^3/_4CH_2Cl_2$) C, H, N.

Preparation of *N*-Methyl-*N*-*tert*-butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (9c). *N*-Methyl-

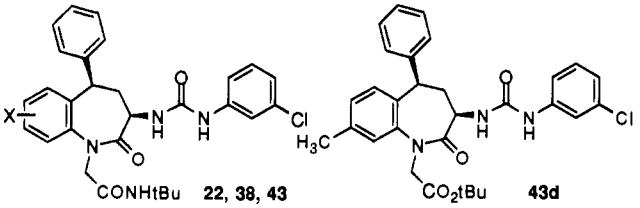
Table 1. *In Vitro* SAR of Benzazepin-2-ones **9**



compd	X	R	IC50 CCK-B[a]	IC50 CCK-A[b]
9a	3-CH_3	OtBu	2.5 ± 0.61	50 ± 21
9b	3-CH_3	NHtBu	10.1 ± 2.7	288 ± 102
9c	3-Cl	N(CH_3)tBu	1.5 ± 0.41	4.2 ± 1.8
9d	3-Cl	NH(1,1-(CH_3)$_2$)Et	7.6 ± 1.2	144 ± 32
9e	3-Cl	NH(1-CH_3)cyclohexyl	3.8 ± 0.80	467 ± 29
9f	3-Cl	NH(1,1-(CH_3)$_2$)benzyl	10.6 ± 1.3	460 ± 121
9g	3-OCH_3	NHtBu	30.4 ± 12.7	166 ± 81
9h	3-Cl	NHtBu	4.3 ± 1.8	144 ± 59
9i	4-Cl	NHtBu	43 ± 10.5	399 ± 150
9j	2-CH_3	NHtBu	55 ± 17.4	1,467 ± 176
9k	4-CH_3	NHtBu	35 ± 8.7	1,143 ± 361
1			8.1 ± 1.5	86 ± 27

[a] Binding affinity for the CCK-B receptor in guinea pig cortex using [^{125}I]BH-CCK-8 as ligand, given in nM units. IC_{50} values were determined from six-point concentration–response curves with each concentration in triplicate. Mean ± SEM values from three separate experiments are given for each compound. [b] Binding affinity for the CCK-A receptor in guinea pig pancreas using [^{125}I]BH-CCK-8 as ligand, given in nM units. IC_{50} values were determined from six-point concentration–response curves with each concentration in triplicate. Mean ± SEM values from three separate experiments are given for each compound.

Table 2. *In Vitro* SAR of 7- and 8-Substituted Benzazepin-2-ones **22**, **38**, **43**, **4**, and **82**



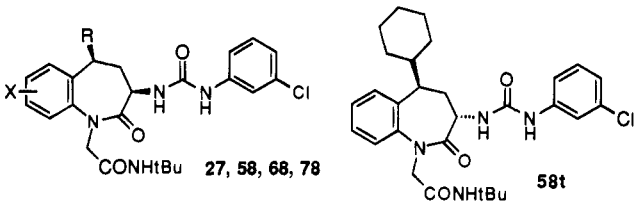
compd	X	IC50 CCK-B[a]	IC50 CCK-A[b]
22a	7-CH_3	32 ± 6.4	317 ± 49
22b	7-Cl	24 ± 7.8	287 ± 148
38	9-CH_3	2.2 ± 0.35	77 ± 18
43a	8-CH_3	1.0 ± 0.23	130 ± 25
43b	8-CH_2CH_3	2.0 ± 0.21	71 ± 18
43c	8-Cl	6.7 ± 2.7	320 ± 81
43d	8-CH_3	2.2 ± 0.59	34 ± 16
4	8-CH_3 (+)	0.48 ± 0.079	176 ± 46
82	8-CH_3 (−)	35.7 ± 4.1	363 ± 64

[a] Binding affinity for the CCK-B receptor in guinea pig cortex using [^{125}I]BH-CCK-8 as ligand, given in nM units. IC_{50} values were determined from six-point concentration–response curves with each concentration in triplicate. Mean ± SEM values from three separate experiments are given for each compound. [b] Binding affinity for the CCK-A receptor in guinea pig pancreas using [^{125}I]BH-CCK-8 as ligand, given in nM units. IC_{50} values were determined from six-point concentration–response curves with each concentration in triplicate. Mean ± SEM values from three separate experiments are given for each compound.

***N*-*tert*-butylchloroacetamide** was prepared according to method B as an oil, which was used directly in the next step: ^{1}H-NMR (δ, $CDCl_3$) 1.33 (s, 9H), 2.87 (s, 3H), 3.97 (s, 2H); ^{13}C-NMR (δ, $CDCl_3$) 27.8, 32.4, 44.5, 57.5, 166.7; IR (cm^{-1}, neat) 1653 (C=O).

***N*-Methyl-*N*-*tert*-butyliodoacetamide** was prepared according to method B as an oil in 63% overall yield for two steps: ^{1}H-NMR (δ, $CDCl_3$) 1.35 (s, 3H), 2.87 (s, 3H), 3.67 (s, 2H); ^{13}C-NMR (δ, $CDCl_3$) 27.8, 33.8, 33.9, 57.5, 168.0; IR (cm^{-1}, neat) 1642 (C=O).

Table 3. *In Vitro* SAR of 5-Substituted Benzazepin-2-ones **27**, **58**, **68**, and **78**



compd	X	R	IC50 CCK-B[a]	IC50 CCK-A[b]
27	H	(3-Cl)phenyl	4.0 ± 0.91	69 ± 34
58c	H	cyclohexyl	1.07 ± 0.14	171 ± 87
58t	H	cyclohexyl (*trans*)	130 ± 30	>10000
68a	8-CH_3	cyclohexyl	0.60 ± 0.25	560 ± 203
68b	8-CH_3	benzyl	1.4 ± 0.06	>10000
68c	8-CH_3	2-propyl	3.4 ± 1.3	72 ± 14
78	8-CH_3	4-tolyl	7.7 ± 2.7	417 ± 181

[a] Binding affinity for the CCK-B receptor in guinea pig cortex using [^{125}I]BH-CCK-8 as ligand, given in nM units. IC_{50} values were determined from six-point concentration–response curves with each concentration in duplicate. Mean ± SEM values from three separate experiments are given for each compound. [b] Binding affinity for the CCK-A receptor in guinea pig pancreas using [^{125}I]BH-CCK-8 as ligand, given in nM units. IC_{50} values were determined from six-point concentration–response curves with each concentration in duplicate. Mean ± SEM values from three separate experiments are given for each compound.

Table 4. Physical Properties for Compounds **9**, **22**, **27**, **38**, **43**, **58**, **68**, and **78**

compd	formula	mp, °C	yield, %	anal.
9a	$C_{30}H_{33}N_3O_4$	195	30	C,H,N
9b	$C_{30}H_{34}N_4O_3 \cdot {}^1/_2H_2O$	263–266	88	C,H,N
9c	$C_{30}H_{33}ClN_4O_3$	155–162	97	C,H,N
9d	$C_{30}H_{33}ClN_4O_3$	219–222	73	C,H,N
9e	$C_{32}H_{35}ClN_4O_3$	215–220	84	C,H,N
9f	$C_{30}H_{33}N_4O_3Cl \cdot {}^1/_8CH_2Cl_2$	150–160	83	C,H,N
9g	$C_{30}H_{34}N_4O_4 \cdot {}^1/_2H_2O$	254–257	81	C,H,N
9h	$C_{29}H_{31}ClN_4O_3 \cdot {}^1/_5CH_2Cl_2$	264–266	90	C,H,N
9i	$C_{29}H_{31}ClN_4O_3 \cdot {}^1/_2CH_2Cl_2$	247–249	88	C,H,N
9j	$C_{30}H_{34}N_4O_3 \cdot {}^1/_2H_2O$	231–233	85	C,H,N
9k	$C_{30}H_{34}N_4O_3 \cdot {}^3/_4CH_2Cl_2$	235–238	95	C,H,N
22a	$C_{30}H_{33}N_4O_3Cl$	155–165	46	C,H,N
22b	$C_{29}H_{30}N_4O_3Cl_2 \cdot {}^1/_3H_2O$	234–236	83	C,H,N
27	$C_{29}H_{30}N_4O_3Cl_2 \cdot {}^1/_3H_2O$	240–243	84	C,H,N
38	$C_{31}H_{36}N_4O_3Cl$	260–262	77	C,H,N
43a	$C_{30}H_{33}N_4O_3Cl$	155–165	68	C,H,N
43b	$C_{31}H_{35}ClN_4O_3 \cdot {}^1/_4H_2O$	145–150	93	C,H,N
43c	$C_{29}H_{30}ClN_4O_3 \cdot {}^1/_4H_2O$	239–243	37	C,H,N
43d	$C_{30}H_{32}N_3O_4Cl \cdot {}^1/_4H_2O$	230–235	62	C,H,N
58c	$C_{29}H_{37}ClN_4O_3 \cdot {}^1/_4H_2O$	223–226	48	C,H,N
58t	$C_{29}H_{37}ClN_4O_3 \cdot {}^1/_3(C_2H_6Cl_2)$	292–297	17.5	C,H,N
68a	$C_{33}H_{43}ClN_4O_3$	181–184	52	C,H,N
68b	$C_{31}H_{35}ClN_4O_3 \cdot {}^1/_2H_2O$	298–315	80	C,H,N
68c	$C_{27}H_{35}ClN_4O_3 \cdot {}^2/_3H_2O$	272–275	59	C,H,N
78	$C_{31}H_{35}ClN_4O_3 \cdot C_6H_6$	239–241	92	C,H,N

***N*-Methyl-*N*-*tert*-butyl-2-[3-(3-bromo-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (6c)** was prepared according to method A from 3-bromo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one and *N*-methyl-*N*-*tert*-butyliodoacetamide: mp 209–213 °C; 30% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.38 (s, 9H), 2.8–3.0 (m, 2H), 2.93 (s, 3H), 4.60 (dd, J = 8, 11, 1H), 4.62 (AB q, J_{AB} = 15, Δν = 52, 2H), 5.17 (m, 1H), 6.69 (d, J = 8, 1H), 7.03 (m, 1H), 7.1–7.4 (m, 7H); ^{13}C-NMR (δ, $CDCl_3$) 28.2, 31.1, 43.5, 45.8, 47.8, 53.3, 57.4, 122.7, 127.0, 127.2, 127.6, 127.8, 128.6, 128.9, 138.4, 139.8, 141.2, 167.1, 167.4; IR (cm^{-1}, KBr) 1660, 1680 (C=O); EI MS

(rel int) 422/424 (parent, Br^{79}/Br^{81}, 6/5), 328/330 (Br^{79}/Br^{81}, 64/62), 276 (70), 250 (40), 57 (100); HRMS calcd for $C_{23}H_{27}N_2O_2$-Br 442.1256, found 442.125 22. Anal. ($C_{23}H_{27}N_2O_2Br \cdot {}^1/_2H_2O$) C, H, N.

***N*-Methyl-*N*-*tert*-butyl-2-[3-(3-azido-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (7c)** was prepared according to method A: mp 155–158 °C; 81% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.35 (s, 9H), 2.58 (s, 3H), 2.6–3.0 (m, 2H), 3.29 (AB q, J_{AB} = 16, Δν = 335, 2H), 3.93 (m, 1H), 4.22 (m, 1H), 7.0–7.4 (m, 9H); ^{13}C-NMR (δ, $CDCl_3$) 28.2, 30.9, 35.7, 43.9, 52.8, 57.3, 57.8, 126.3, 127.2, 138.3, 128.5, 128.7, 129.0, 130.1, 138.2, 141.4, 141.7, 167.5, 168.9; IR (cm^{-1}, KBr) 2120 (N_3), 1660, 1680 (C=O); EI MS (rel int) 405 (parent, 4), 377 (23), 290 (57), 263 (70), 206 (78), 91 (100). Anal. ($C_{23}H_{27}N_5O_2$) C, H, N.

***N*-Methyl-*N*-*tert*-butyl-2-[3-(3-amino-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (8c)** was prepared according to method A: mp 65–75 °C; 100% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.33 (s, 9H), 2.5–2.6 (m, 2H), 2.56 (s, 3H), 3.25 (AB q, J_{AB} = 16, Δν = 332, 2H), 3.55 (m, 1H), 4.18 (m, 1H), 7.0–7.4 (m, 9H); ^{13}C-NMR (δ, $CDCl_3$) 28.2, 30.8, 39.8, 44.7, 50.4, 52.7, 57.2, 125.0, 125.9, 126.5, 126.7, 128.0, 128.5, 130.0, 130.1, 139.2, 141.9, 142.5, 168.0, 174.5; IR (cm^{-1}, KBr) 1660 broad (C=O); EI MS (rel int) 379 (parent, 10), 237 (60), 208 (55), 188 (100); HRMS calcd for $C_{23}H_{29}N_3O_2$ 379.2260, found 379.226 77. Anal. ($C_{23}H_{29}N_3O_2 \cdot {}^1/_2H_2O$) C, H, N.

***N*-Methyl-*N*-*tert*-butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (9c)** was prepared according to method A: mp 155–162 °C; 97% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.32 (s, 9H), 2.50 (s, 3H), 2.84 (m, 1H), 3.02 (m, 1H), 3.40 (AB q, J_{AB} = 16, Δν = 288, 2H), 4.26 (m, 1H), 4.62 (m, 1H), 6.8–7.6 (m, 14H), 7.96 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 28.2, 30.7, 38.0, 44.5, 49.6, 53.1, 57.5, 117.4, 118.9, 121.5, 124.7, 126.2, 126.6, 127.5, 128.2, 128.8, 129.3, 130.5, 133.8, 138.7, 141.1, 141.3, 142.6, 154.6, 167.0, 172.8; IR (cm^{-1}, KBr) 1650 broad (C=O); FAB MS (rel int) 533 (parent + 1, 14), 446 (80), 293 (54), 237 (52), 220 (98), 194 (100). Anal. ($C_{30}H_{33}N_4O_3Cl$) C, H, N.

Preparation of *N*-(1,1-Dimethylethyl)-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (9d). *N*-(1,1-Dimethylethyl)bromoacetamide was prepared according to method B using bromoacetyl bromide: 75% yield; mp 49–52 °C; ^{1}H-NMR (δ, $CDCl_3$) 0.85 (t, J = 7, 3H), 1.31 (s, 6H), 2.72 (q, J = 7, 2H), 3.78 (s, 3H).

***N*-(1,1-Dimethylethyl)iodoacetamide** was prepared according to method B: 79% yield; mp 65–67 °C; ^{1}H-NMR (δ, $CDCl_3$) 0.84 (t, J = 7, 3H), 2.26 (s, 6H), 2.70 (q, J = 7, 2H), 3.59 (s, 3H).

***N*-(1,1-Dimethylethyl)-2-[3-(3-bromo-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (6d)** was prepared according to method A from 3-bromo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one and *N*-(1,1-dimethylethyl)iodoacetamide: mp 105–110 °C; 86% yield (crystallized from methylene chloride/hexane, the hexane remaining in the analytical sample); ^{1}H-NMR (δ, $CDCl_3$) 0.8–0.9 (m, 3H), 1.28 and 1.29 (s's, 6H), 1.6–1.8 (m, 2H), 2.85 (m, 1H), 3.04 (m, 1H), 4.39 (bs, 2H), 4.56 (dd, J = 7, 12, 1H), 4.65 (m, 1H), 6.04 (bs, 1H), 6.68 (d, J = 8, 1H), 7.06 (t, J = 7, 1H), 7.2–7.4 (m, 7H); ^{13}C-NMR (δ, $CDCl_3$) 26.3, 32.9, 44.0, 45.6, 47.1, 54.3, 54.8, 123.2, 127.4, 127.8, 127.9, 128.1, 128.7, 128.8, 129.1, 137.6, 139.1, 141.0, 167.0, 168.1; IR (cm^{-1}, KBr) 1680, 1670 broad (C=O); EI MS (rel int) 442/444 (parent, Br^{79}/Br^{81}, 10/8), 336 (35), 276 (100), 250 (90); HRMS calcd for $C_{23}H_{27}N_2O_2$-Br 442.1256, found 442.124 27. Anal. ($C_{23}H_{27}N_2O_2Br \cdot {}^1/_3(C_6H_{14})$) C, H, N.

***N*-(1,1-Dimethylethyl)-2-[3-(3-azido-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (7d)** was prepared according to method A: mp 60–70 °C; 98% yield, as a mixture of diastereomers; ^{1}H-NMR (δ, $CDCl_3$) 0.82 (m, 3H), 1.2–1.3 (s's, 6H), 1.6–1.8 (m, 2H), 2.4–2.5 and 2.8–3.0 (m's, 2H), 3.08 and 4.40 (AB q's, J_{AB} = 15 and 15, Δν = 297 and 32, 2H), 3.8–4.0 (m's, 1H), 4.3 and 4.66 (m's, 1H), 6.08 (broad m, 1H), 6.67 (d, J = 7, 1H), 7.0–7.5 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 26.2, 26.3, 32.7, 32.8, 39.7, 42.0, 54.0, 54.1, 54.3, 54.6, 58.3, 59.0, 123.1, 126.1, 127.3, 127.4, 127.8, 127.9, 128.0, 128.5, 128.6, 128.7, 128.8, 129.2, 129.3, 138.0, 139.3, 140.3, 167.0, 170.4; IR (cm^{-1}, KBr) 2110 (N_3), 1680 broad (C=O); FAB MS (rel int) 406 (parent + 1, 100), 380 (50), 319 (77), 194 (40); HRMS calcd for $C_{23}H_{27}N_5O_2$ 405.2165, found 405.217 61.

***N*-(1,1-Dimethylethyl)-2-[3-(3-amino-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (8d)** was prepared according to method A: mp 268–273 °C; 67% yield, crystallized from methylene chloride/isopropyl ether, as a mixture of diastereomers; ^{1}H-NMR (δ, $CDCl_3$) 0.75 (t, J = 7, 3H), 1.2–1.3 (s's, 6H), 1.64 (m, 2H), 2.2–2.5 (m's, 1H), 3.12 (m, 1H), 3.15 and 4.44 (AB q's, J_{AB} = 15 and 15, Δν = 220 and 40, 2H), 3.93 (m, 1H), 4.23 and 4.70 (m's, 1H), 6.64 (d, J = 7, 1H), 7.0–7.5 (m, 8H); IR (cm^{-1}, KBr) 1650, 1680 (C=O); FAB MS (rel int) 380 (parent + 1, 100), 293 (62); HRMS calcd for $C_{23}H_{29}N_3O_2$ 379.2260, found 379.227 23. Anal. ($C_{23}H_{29}N_3O_2 \cdot CH_2Cl_2$) C, H, N.

***N*-(1,1-Dimethylethyl)-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (9d)** was prepared according to method A: mp 219–222 °C; 73% yield; ^{1}H-NMR (δ, $CDCl_3$) 0.74 (t, J = 7, 3H), 1.23 (s, 9H), 1.64 (q, J = 7, 2H), 2.94 (m, 1H), 3.01 (m, 1H), 3.32 (AB q, J_{AB} = 16, Δν = 274, 2H), 4.15 (m, 1H), 4.59 (m, 1H), 5.73 (bs, 1H), 6.5–7.4 (m, 12H), 7.57 (bs, 1H), 7.97 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 8.4, 26.2, 32.9, 36.9, 44.5, 50.4, 53.2, 54.7, 117.0, 118.9, 119.0, 122.1, 124.3, 124.4, 126.3, 126.4, 126.6, 127.8, 128.3, 129.1, 129.5, 130.9, 134.3, 138.2, 140.7, 141.1, 141.8, 155.1, 167.2, 173.2; IR (cm^{-1}, KBr) 1650 broad (C=O); FAB MS (rel int) 533/535 (parent + 1, Cl^{35}/Cl^{37}, 34/13), 446 (75), 293 (60), 220 (86), 194 (100). Anal. ($C_{30}H_{33}N_4O_3Cl$) C, H, N.

Preparation of *N*-(1-Methylcyclohexyl)-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (9e). *N*-(1-Methylcyclohexyl)bromoacetamide was prepared according to method B using bromoacetyl bromide and 1-methylcyclohexylamine, in 28% yield as an oil: ^{1}H-NMR (δ, $CDCl_3$) 1.2–1.6 (m, 8H), 1.31 (s, 3H), 1.95 (m, 2H), 3.76 (s, 2H); FAB MS (rel int) 234/236 (parent, Br^{79}/Br^{81}, 98/95), 138/140 (Br^{79}/Br^{81}, 60/57), 119 (100).

***N*-(1-Methylcyclohexyl)iodoacetamide** was prepared according to method B: 84% yield; mp 95–98 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.29 (s, 3H), 1.3–1.6 (m, 8H), 1.96 (m, 2H), 3.61 (s, 2H), 5.90 (bs, 1H, N*H*); IR (cm^{-1}, KBr) 1637 (C=O); ^{13}C-NMR (δ, $CDCl_3$) 21.9, 25.5, 26.0, 36.4, 54.0, 165.9; FAB MS (rel int) 282 (parent + 1, 100), 186 (53), 156 (68), 119 (62).

***N*-(1-Methylcyclohexyl)-2-(3-bromo-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (6e)** was prepared according to method A using *N*-(1-methylcyclohexyl)iodoacetamide to alkylate 3-bromo-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine in 75% yield: mp 164–168 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.35 (s, 9H), 1.46 (s, 3H), 1.2–1.5 and 1.9–2.1 (m, 10H), 2.62 and 2.79 (multiplets for 2 diastereomers, 1H), 2.92 (m, 1H), 4.2–4.7 (m, 4H), 6.0 and 6.11 (singlets, 1H), 6.6–7.4 (m, 9H); ^{13}C-NMR (δ, $CDCl_3$) 121.9, 22.0, 25.5, 26.4, 36.3, 36.9, 43.0, 43.1, 44.1, 44.8, 47.1, 53.7, 54.8, 55.1, 56.5, 123.2, 127.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.7, 128.8, 129.0, 137.5, 137.7, 139.0, 140.7, 141.1, 167.1, 168.2, 168.7; IR (cm^{-1}, KBr) 1660 broad (C=O); MS (rel int) 468/470 (parent for Br^{79}/Br^{81}, 1/1), 276 (50), 250 (51), 165 (40), 97 (38), 55 (100).

***N*-(1-Methylcyclohexyl)-2-(3-azido-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (7e)** was prepared according to method A in 41% yield as an oil: ^{1}H-NMR (δ, $CDCl_3$) 1.29 (s, 9H), 1.43 (s, 3H), 1.1–1.6 and 1.8–2.0 (m, 10H), 2.76 (m, 1H), 2.92 (m, 1H), 3.09 (AB q, J_{AB} = 15, Δν = 317, 2H), 3.97 (m, 1H), 4.20 (m, 1H), 6.18 (bs, 1H), 6.9–7.5 (m, 9H); ^{13}C-NMR (δ, $CDCl_3$) 21.8, 22.0, 25.5, 26.4, 35.7, 35.8, 36.0, 36.1, 36.3, 36.9, 37.0, 43.7, 53.4, 54.7, 58.4, 125.5, 125.6, 125.7, 125.8, 125.9, 126.0, 126.2, 126.5, 126.6, 126.7, 127.3, 127.5, 127.6, 127.7, 128.0, 128.5, 128.7, 129.2, 129.3, 130.3, 130.4, 137.9, 141.0, 141.1, 168.0, 170.0; IR (cm^{-1}, KBr) 2100 (N_3) and 1675 broad (C=O); FAB MS (rel

int) 432 (parent + 1, 32), 406 (70), 319 (100), 293 (92), 194 (90), 91 (92); HRMS calcd for $C_{25}H_{29}N_5O_2$ 431.2315, found 431.231 35.

***N*-(1-Methylcyclohexyl)-2-(3-amino-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (8e)** was prepared according to method A in 69% yield as a white foam: ^{1}H-NMR (δ, $CDCl_3$) 1.26 (s, 9H), 1.39 (s, 3H), 1.0–1.7 and 1.8–2.0 (m, 10H), 2.22 (bs, 2H, N*H*$_2$), 2.5 (m, 1H), 2.78 (m, 1H), 3.08 (AB q, J_{AB} = 15, Δν = 305, 2H), 3.48 (m, 1H), 4.10 (m, 1H), 6.10 (bs, 1H), 6.9–7.4 (m, 9H); ^{13}C-NMR (δ, $CDCl_3$) 21.9, 25.5, 26.4, 31.5, 36.2, 36.8, 39.7, 44.5, 50.7, 53.4, 54.4, 125.3, 125.4, 125.5, 126.2, 127.2, 128.3, 128.5, 128.8, 130.2, 138.7, 141.6, 141.8, 168.3, 175.1; IR (cm^{-1}, KBr) 1660 broad (C=O); FAB MS (rel int) 406 (parent + 1, 84), 293 (100), 237 (38), 194 (43); HRMS calcd for $C_{25}H_{31}N_3O_2$ 405.2409, found, 405.238 07.

***N*-(1-Methylcyclohexyl)-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]-ethanoic acid amide (9e)** was prepared according to method A: mp 215–220 °C; 84% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.28 (s, 9H), 1.36 (s, 3H), 1.2–1.5 (m, 6H), 1.8–2.0 (m, 4H), 2.9–3.0 (m, 2H), 3.33 (AB q, J_{AB} = 16, Δν = 284, 2H), 4.26 (d, J = 7, 1H), 4.63 (m, 1H), 5.79 (bs, 1H), 6.6–7.6 (m, 13H), 7.99 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 22.0, 22.1, 25.4, 25.9, 36.4, 36.7, 36.9, 44.5, 53.4, 54.1, 117.1, 119.1, 122.2, 124.4, 124.5, 126.3, 126.5, 126.6, 127.8, 128.4, 129.1, 129.6, 130.8, 134.3, 138.2, 140.7, 141.1, 141.7, 155.1, 167.4, 173.2; IR (cm^{-1}, KBr) 1650 broad (C=O); FAB MS (rel int) 559/561 (parent + 1, Cl^{35}/Cl^{37}, 21/8), 446 (69), 293 (55), 237 (58), 220 (92), 194 (100), 97 (80). Anal. ($C_{32}H_{35}N_4O_3Cl$) C, H, N.

Preparation of *N*-(1,1-Dimethylbenzyl)-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (9f). *N*-(1,1-Dimethylbenzyl)bromoacetamide was prepared according to method B using bromoacetyl bromide, as an oil, which was used directly in the next step: ^{1}H-NMR (δ, $CDCl_3$) 1.69 (s, 6H), 3.76 (s, 2H), 6.72 (bs, 1H, N*H*), 7.1–7.4 (m, 5H).

***N*-(1,1-Dimethylbenzyl)iodoacetamide** was prepared according to method B: 80% yield; mp 130–135 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.62 (s, 6H), 3.51 (s, 2H), 6.76 (bs, 1H, N*H*), 7.2–7.4 (m, 5H); ^{13}C-NMR (δ, $CDCl_3$) 28.8, 56.3, 124.7, 126.8, 128.4, 146.4, 166.1; IR (cm^{-1}, KBr) 1640 broad (C=O); EI MS (rel int) 303 (parent, 4), 288 (20), 176 (38), 120 (100), 118 (87). Anal. Calcd for $C_{11}H_{14}INO$: C, 43.58; H, 4.65; N, 4.62. Found: C, 43.53; H, 4.23; N, 4.76.

***N*-(1,1-Dimethylbenzyl)-2-[3-(3-bromo-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (6f)** was prepared according to method A from 3-bromo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one and *N*-(1,1-dimethylbenzyl)iodoacetamide: mp 100–104 °C; 56% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.67 (s, 3H), 1.71 (s, 3H), 2.65, 2.82, and 2.96 (m's, 2H), 4.4–4.6 (m, 4H), 6.67 (d, J = 7, 1H), 6.75 (bs, 1H), 7.0–7.4 (m, 13H); ^{13}C-NMR (δ, $CDCl_3$) 26.9, 29.0, 29.3, 42.9, 44.0, 44.8, 54.3, 54.5, 56.2, 56.5, 123.2, 123.3, 124.7, 126.6, 127.3, 127.4, 127.9, 128.0, 128.3, 128.8, 128.9, 138.0, 139.0, 146.6, 166.6, 168.8; IR (cm^{-1}, KBr) 1660, 1680 (C=O); EI MS (rel int) 491/493 (parent, Br^{79}/Br^{81}, 10/9), 356/358 (Br^{79}/Br^{81}, 44/42), 312 (100); HRMS calcd for $C_{27}H_{28}N_2O_2Br$ 491.1327, found 491.135 44.

***N*-(1,1-Dimethylbenzyl)-2-[3-(3-azido-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (7f)** was prepared according to method A as a foam in 44.5% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.61 (s, 3H), 1.66 (s, 3H), 2.80 (m, 1H), 2.94 (m, 1H), 3.13 (AB q, J_{AB} = 16, Δν = 286), 3.97 (m, 1H), 4.19 (m, 1H), 6.69 (bs, 1H), 7.0–7.5 (m, 14H); ^{13}C-NMR (δ, $CDCl_3$) 28.7, 29.5, 35.7, 43.7, 54.5, 58.4, 124.6, 126.1, 126.6, 127.7, 127.8, 128.4, 128.5, 129.2, 129.3, 130.2, 130.3, 137.9, 141.0, 146.5, 167.4, 170.0; IR (cm^{-1}, KBr) 2100 (N_3), 1670 broad (C=O); EI MS (rel int) 454 (parent + 1, 7), 336 (18), 319 (17), 119 (100); HRMS calcd for $C_{27}H_{27}N_5O_2$ 453.2159, found 453.215 44.

***N*-(1,1-Dimethylbenzyl)-2-[3-(3-amino-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (8f)** was prepared according to method A: mp 185–195 °C; 97% yield, crystallized from methylene chloride/hexane; ^{1}H-NMR (δ, $CDCl_3$) 1.53 (s, 6H), 2.90 (m, 1H), 3.10 (m, 1H), 3.15 (AB q, J_{AB} = 16, Δν = 315), 3.91 (m, 1H), 4.01 (m, 1H), 6.8–7.4 (m, 14H); ^{13}C-NMR (δ, $CDCl_3$) 29.3, 29.5, 34.1, 43.7, 50.3, 53.1, 56.2, 124.8, 125.3, 125.4, 126.4, 126.7, 128.0, 128.1, 128.3, 128.6, 129.1, 130.8, 138.0, 140.2, 140.8, 146.8, 167.8, 168.8; IR (cm^{-1}, KBr) 1670 broad (C=O); FAB MS (rel int) 428 (parent + 1, 10), 310 (16), 293 (19), 194 (17), 119 (100); HRMS calcd for $C_{27}H_{30}N_3O_2$ 428.2338, found 428.234 37. Anal. ($C_{27}H_{29}N_3O_2 \cdot CH_2Cl_2 \cdot {}^1/_4H_2O$) C, H, N.

***N*-(1,1-Dimethylbenzyl)-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]-ethanoic acid amide (9f)** was prepared according to method A: mp 150–160 °C from methylene chloride/hexane; 83% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.60 (s, 3H), 1.64 (s, 3H), 2.8–2.9 (m, 2H), 3.36 (AB q, J_{AB} = 17, Δν = 298, 2H), 4.26 (d, J = 7, 1H), 4.58 (dd, J = 7, 12, 1H), 6.6–6.9 and 7.0–7.4 (m, 16H), 7.89 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 29.0, 29.3, 36.6, 44.5, 50.4, 53.1, 56.1, 117.1, 118.9, 119.0, 122.1, 124.6, 124.7, 126.3, 126.6, 127.8, 128.3, 128.4, 129.0, 129.6, 130.9, 134.1, 138.2, 140.6, 141.0, 141.7, 146.4, 155.2, 167.3, 173.3; IR (cm^{-1}, KBr) 1650 broad (C=O); FAB MS (rel int) 581 (parent + 1, Cl^{35}/Cl^{37}, 7/3), 446 (54), 220 (40), 194 (44), 119 (100); HRMS calcd for $C_{30}H_{34}N_4O_3Cl$ 581.2312, found 581.234 46. Anal. ($C_{30}H_{33}N_4O_3Cl \cdot {}^1/_8CH_2Cl_2$) C, H, N.

Method C. *N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-7-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (22a). 3-Carbethoxy-4-phenyl-4-(3-methylphenyl)but-3-enoic Acid (10a). To a 250 mL round-bottomed flask equipped with condenser and N_2 inlet were added 100 mL of *tert*-butyl alcohol, 12.57 g (112 mmol) of potassium *tert*-butoxide, 20 g (102 mmol) of 3-methylbenzophenone, and 21.31 g (122 mmol) of diethyl succinate. The reaction mixture was refluxed for 14 h, cooled, acidified with HCl, and then partitioned between water and ether. The organic layer was washed with 1 N aqueous sodium hydroxide solution, which was then acidified and extracted into ether. The organic layer was dried and concentrated to an orange oil which was used directly to prepare the following.

4-Phenyl-4-(3-methylphenyl)but-3-enoic Acid (11a). The above oil was heated to reflux in a solution of 60 mL of acetic acid, 60 mL of 48% hydrobromic acid, and 50 mL of additional acetic acid for solubility for 14 h. The brown oil that separated on cooling was isolated, dissolved in ethyl acetate, and washed with water and then with 2% aqueous sodium hydroxide solution. The basic aqueous phase was acidified, extracted into ethyl acetate, dried, and concentrated. The product was a mixture of olefin isomers by NMR, which showed two peaks for the methyl group at 2.27 and 2.29 ppm: ^{1}H-NMR (δ, $CDCl_3$) 2.27 and 2.29 (s, 3H), 3.19 (m, 2H), 6.18 (t, J = 7, 1H), 6.8–7.4 (m, 9H).

4-Phenyl-4-(3-methylphenyl)butanoic Acid (12a). The above oil (25.7 g) was hydrogenated at 30 psi of hydrogen in ethyl acetate with 1.25 g of 10% palladium on carbon for 2 h. Filtration through Celite and concentration, followed by chromatography on silica gel using methanol/methylene chloride as eluant, afforded an oil which was crystallized from heptane: 4.70 g (18% overall); mp 96–100 °C; ^{1}H-NMR (δ, $CDCl_3$) 2.35 (s, 3H), 2.2–2.3 (m, 4H), 3.95 (t, J = 7, 1H), 7.0–7.4 (m, 9H); ^{13}C-NMR (δ, $CDCl_3$) 21.6, 30.3, 32.6, 50.4, 124.8, 126.5, 127.3, 127.9, 128.5, 128.6, 138.2, 143.9, 144.2, 180.3; IR (cm^{-1}, KBr) 1720 (C=O); MS (rel int) 254 (parent, 23), 182 (100), 165 (23), 32 (36), 28 (100). Anal. ($C_{17}H_{18}O_2$) C, H, N.

4-Phenyl-6-methyl-1,2,3,4-tetrahydronaphth-1-one (13a). To a 250 mL round-bottomed flask equipped with condenser and N_2 inlet were added 8.2 g (32.3 mmol) of **12a**, 54 mL of toluene, and 4.6 g (38.64 mmol) of thionyl chloride. The reaction mixture was refluxed for 1 h, cooled, and concentrated. The oil was dissolved in 15 mL of carbon disulfide and added dropwise to a slurry of 29.98 g (225 mmol) of aluminum chloride in 50 mL of carbon disulfide which had been cooled to 0 °C. The reaction mixture was allowed to stand for 16 h, poured onto ice, and partitioned between water and ethyl acetate. The organic phase was washed with water, aqueous sodium bicarbonate solution, and water, dried, and evaporated. The oil was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford an oil: 4.03 g (53%); ^{1}H-NMR (δ, $CDCl_3$) 2.28 (s, 3H), 2.2–2.7 (m, 4H), 4.24 (m, 1H), 6.8–7.4

(m, 7H), 8.02 (d, J = 7, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.8, 31.9, 36.4, 36.5, 45.2, 126.8, 128.1, 128.5, 128.6, 129.9, 130.6, 143.8, 144.5, 146.2, 197.8; IR (cm^{-1}, KBr) 1680 (C=O); MS (rel int) 236 (parent, 96), 208 (92), 194 (42), 166 (43).

4-Phenyl-6-methyl-1,2,3,4-tetrahydronaphth-1-one Oxime (15a). To a 125 mL round-bottomed flask equipped with condenser and N_2 inlet were added 4.3 g (18.29 mmol) of **13a**, 46 mL of methanol, 2.95 g (29.26 mmol) of triethylamine, and 2.02 g (29.26 mmol) of hydroxylamine hydrochloride. The reaction was stirred at room temperature for 3 days, evaporated, and partitioned between ethyl acetate and water, and the aqueous layer was extracted with fresh ethyl acetate. The combined organic layer was dried over sodium sulfate and evaporated to an oil, 4.57 g (100%): ^{1}H-NMR (δ, $CDCl_3$) 2.1–2.3 (m, 2H), 2.28 (s, 3H), 2.8–3.0 (m, 2H), 4.17 (m, 1H), 6.8–7.4 (m, 7H), 7.95 (d, J = 7, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.1, 21.4, 29.6, 45.0, 126.5, 128.0, 128.1, 128.5, 129.2, 129.9, 139.7, 141.4, 144.0, 155.3; IR (cm^{-1}, KBr) 1610 (C=N); MS (rel int) 251 (parent, 94), 234 (32), 156 (17), 91 (17); HRMS calcd for $C_{17}H_{17}NO$ 251.1310, found 251.130 22.

5-Phenyl-7-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (17a). To a 250 mL round-bottomed flask equipped with N_2 inlet were added 4.5 g (18.3 mmol) of **15a** and 59.45 g of polyphosphoric acid. The mixture was heated in a 130 °C oil bath for 25 min, poured onto ice, and stirred until homogeneous. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford an oil, 2.20 g (49%), which could be crystallized from methylene chloride and isopropyl ether to afford a solid: mp 169–173 °C; ^{1}H-NMR (δ, $CDCl_3$) 2.16 (s, 3H), 2.4–2.6 (m, 4H), 4.40 (m, 1H), 6.6 and 7.0–7.4 (m, 8H), 9.15 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.1, 32.9, 33.9, 45.0, 121.9, 127.0, 127.9, 128.6, 129.0, 129.1, 135.0, 135.2, 136.5, 141.2, 175.8; IR (cm^{-1}, KBr) 1680 (C=O); MS (rel int) 252 (parent + 1, 100), 196 (10), 147 (10), 135 (14), 119 (13), 103 (12). Anal. ($C_{17}H_{17}NO$) C, H, N.

3-Bromo-5-phenyl-7-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (18a) was prepared according to method A: mp 205–211 °C; 62% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.13 (s, 3H), 2.83 (m, 1H), 3.09 (m, 1H), 4.42 (m, 1H), 4.62 (m, 1H), 6.6 and 7.0–7.4 (m, 8H), 8.99 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.1, 45.0, 46.1, 47.3, 122.5, 127.4, 128.3, 128.6, 128.8, 128.9, 133.5, 133.6, 135.8, 136.4, 139.3, 169.3; IR (cm^{-1}, KBr) 1678 (C=O); MS (rel int) 330/332 (parent, Br^{79}/Br^{81}, 100/98), 251 (26), 137 (32), 119 (32), 85 (27). Anal. ($C_{17}H_{16}NOBr$) C, H, N.

***N-tert*-Butyl-2-(3-bromo-2-oxo-5-phenyl-7-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (19a)** was prepared according to method A: mp 129–133 °C; 93% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.33 (s, 9H), 2.14 (s, 3H), 2.83 (m, 1H), 3.01 (m, 1H), 4.3–4.5 (m, 2H), 4.59 (m, 1H), 4.66 (m, 1H), 6.14 (bs, 1H), 6.48 (bs, 1H), 7.0–7.4 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 21.2, 28.7, 43.9, 45.7, 47.3, 51.5, 54.8, 123.0, 127.3, 128.3, 128.7, 128.8, 128.9, 129.0, 137.4, 137.5, 138.4, 139.1, 167.1, 168.2; IR (cm^{-1}, KBr) 1662 (C=O); MS (rel int) 443/445 (parent, Br^{79}/Br^{81}, 90/92), 370/372 (Br^{79}/Br^{81}, 100/98), 290 (50), 262 (45), 134 (65). Anal. ($C_{23}H_{27}N_2O_2Br^1/_3H_2O$) C, H, N.

***N-tert*-Butyl-2-(3-azido-2-oxo-5-phenyl-7-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (20a)** was prepared according to method A as a mixture of diastereomers in 81% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.27, 1.32 (s's, 9H), 2.12, 2.37 (s's, 3H), 2.78 (m, 1H), 2.95 (m, 1H), 2.98 (AB q, J_{AB} = 15, $\Delta\nu$ = 279, part of 2H), 3.82, 3.96, 4.06, and 4.64 (m's, 2H), 4.35 (s, rest of 2H), 6.17 (bs, 1H), 6.45 (bs, 1H), 7.0–7.4 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 21.2, 28.6, 28.7, 35.5, 39.8, 41.9, 43.7, 51.3, 51.5, 54.6, 58.3, 59.0, 60.4, 123.0, 125.6, 126.1, 126.5, 127.3, 127.33, 127.4, 128.2, 128.3, 128.4, 128.5, 128.6, 128.65, 128.7, 128.8, 128.9, 129.58, 129.64, 130.9, 137.2, 137.6, 137.7, 138.5, 139.4, 141.1, 167.1, 167.9, 169.9, 170.4; IR (cm^{-1}, KBr) 2098 (N_3), 1660 (C=O); MS (rel int) 406 (parent + 1, 74), 380 (43), 347 (41), 333 (100), 249 (45), 234 (62), 222 (77), 220 (74), 208 (79), 144 (51), 132 (41), 105 (47), 91 (90); HRMS calcd for $C_{23}H_{27}N_5O_2$ 405.2165, found 405.216 22.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-phenyl-7-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (21a)** was prepared according to method A: mp 100–110 °C, as a mixture of diastereomers in 29% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.24, 1.31 (s's, 9H), 2.11, 2.35 (s's, 3H), 2.62 (bs, 2H), 2.6–2.8 (m, 2H), 3.2–3.4 (m, 2H), 4.0–4.5 (m, 4H), 6.09 (bs, 1H), 6.4 (bs, 1H), 7.0–7.4 (m, 8H); IR (cm^{-1}, KBr) 1660 (C=O); MS (rel int) 379 (parent, 2), 336 (17), 235 (16), 202 (22), 32 (35), 28 (100); HRMS calcd for $C_{23}H_{29}N_3O_2$ 379.2260, found 379.228 48. Anal. ($C_{23}H_{29}N_3O_2 \cdot {}^2/_3H_2O$) C, H; N: Δ 0.69.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-7-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (22a)** was prepared according to method A as a mixture of diastereomers, one of which precipitated from the reaction mixture (more polar); the desired *cis*, less polar, isomer was purified by chromatography, mp 155–165 °C, 46% yield. Spectral data for *cis* isomer: ^{1}H-NMR (δ, $CDCl_3$) 1.28 (s, 9H), 2.39 (s, 3H), 2.8–3.0 (m, 2H), 3.28 (AB q, J_{AB} = 16, $\Delta\nu$ = 281, 2H), 4.11 (m, 1H), 4.38 (m, 1H), 5.83 (bs, 1H), 6.6–7.2 (m, 12H), 7.57 (bs, 1H), 7.98 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 28.7, 36.8, 44.4, 50.4, 51.8, 53.2, 116.9, 122.1, 126.3, 126.5, 128.3, 129.5, 131.5, 134.3, 137.7, 137.8, 137.9, 138.4, 140.7, 141.9, 155.1, 167.4, 173.3; IR (cm^{-1}, KBr) 1640 broad (C=O); FAB MS (rel int) 533/535 (parent + 1, Cl^{35}/Cl^{37}, 37/15), 460/462 (81/31), 380 (33), 307 (61), 251 (61), 234 (100), 222 (62), 208 (99), 91 (51). Anal. ($C_{30}H_{33}N_4O_3Cl$) C, H, N.

Preparation of *N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (22b) and *N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-(3-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (27). 3-Carbethoxy-4-phenyl-4-(3-chlorophenyl)but-3-enoic acid (10b) was prepared according to method C as an oil, which was used directly to prepare the following.

4-Phenyl-4-(3-chlorophenyl)but-3-enoic acid (11b) was prepared according to method C in 89% overall yield as an oil, which was used directly in the next step: ^{1}H-NMR (δ, $CDCl_3$) 3.21 (m, 2H), 6.23 (m, 1H), 7.0–7.4 (m, 9H).

4-Phenyl-4-(3-chlorophenyl)butanoic acid (12b) was prepared according to method C in 71% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.28 (m, 2H), 2.34 (m, 2H), 3.92 (m, 1H), 7.0–7.4 (m, 9H).

4-Phenyl-6-chloro-1,2,3,4-tetrahydronaphth-1-one (13b) and **4-(3-chlorophenyl)-1,2,3,4-tetrahydronaphth-1-one (14)** were prepared according to method C as an inseparable mixture in 53% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.10 (m, 1H), 2.39 (m, 1H), 2.58 (m, 1H), 4.20 (m, 1H), 6.9–7.4 (m, 7H), 8.03 (d, J = 9) and 8.10 (dd, J = 2, 8) (1H for the two isomers), which was converted to the oximes according to method C and separated by column chromatography.

4-Phenyl-6-chloro-1,2,3,4-tetrahydronaphth-1-one oxime (15b): oil; 27% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.0–2.3 (m, 2H), 2.77 (t, J = 7, 2H), 4.07 (m, 1H), 6.8–7.3 and 7.86 (m, 8H).

4-(3-Chlorophenyl)-1,2,3,4-tetrahydronaphth-1-one oxime (16): mp 129–131 °C; 28% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.56 (bs, 1H), 2.0–2.3 (m, 2H), 2.7–2.9 (m, 2H), 4.18 (m, 1H), 6.8–7.4 and 8.0 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 21.2, 29.3, 44.8, 124.2, 126.7, 127.2, 128.6, 129.3, 129.8, 130.7, 134.5, 140.7, 146.0, 154.9; IR (cm^{-1}, KBr) 1598 (C=N); MS (rel int) 271/273 (parent, Cl^{35}/Cl^{37}, 100/35), 254 (42), 217 (24), 190 (29). Anal. ($C_{16}H_{14}NOCl$) C, H, N.

Preparation of *N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (22b). 5-Phenyl-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (17b) was prepared according to method C: mp 184–186 °C; 58% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.49 (m, 4H), 4.33 (m, 1H), 6.71 (bs, 1H), 7.0–7.5 (m, 7H), 9.2–9.4 (broad multiplet, 1H); ^{13}C-NMR (δ, $CDCl_3$) 32.8, 33.7, 45.1, 123.2, 127.4, 128.8, 131.0, 136.1, 140.1, 175.7; IR (cm^{-1}, KBr) 1680 (C=O); EI MS (rel int) 271/273 (parent, Cl^{35}/Cl^{37}, 20/7), 216/218 (Cl^{35}/Cl^{37}, 100/35), 180 (30). Anal. ($C_{16}H_{14}NOCl$) C, H, N.

3-Bromo-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (18b) was prepared according to method A: mp 220–223 °C; 56% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.81 (m, 1H), 3.05 (m, 1H), 4.35 (m, 1H), 4.54 (dd, J = 8, 12, 1H), 6.66 and 7.0–7.4 (m's, 9H); ^{13}C-NMR (δ, $CDCl_3$) 45.1, 45.7, 46.6,

46.7, 123.7, 127.8, 127.9, 128.2, 128.3, 128.4, 128.6, 128.7, 128.8, 129.0, 129.1, 132.0, 134.7, 137.8, 138.3, 168.8; IR (cm^{-1}, KBr) 1690 (C=O); FAB MS (rel int) 351 (parent, 45), 271 (60), 216 (100), 180 (70), 82 (80). Anal. ($C_{16}H_{13}NOClBr$) C, H, N.

***N-tert*-Butyl-2-(3-bromo-2-oxo-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (19b)** was prepared according to method A: mp 125–130 °C (from cyclohexane); 64% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.39 (s, 9H), 2.83 (m, 1H), 2.97 (m, 1H), 4.41 (m, 2H), 4.54 (dd, J = 8, 12, 1H), 4.72 (m, 1H), 5.99 and 6.66 (bs's, 1H), 7.1–7.4 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 28.7, 43.5, 44.0, 45.4, 46.7, 51.7, 54.6, 123.3, 124.7, 127.2, 127.6, 127.7, 128.0, 128.1, 128.2, 128.7, 129.0, 130.0, 133.1, 138.3, 139.6, 139.8, 166.7, 167.8; IR (cm^{-1}, KBr) 1670, 1680 (C=O); FAB MS (rel int) 464 (parent, 5), 383 (15), 356 (62), 310 (85), 284 (77), 57 (100). Anal. ($C_{22}H_{24}N_2O_2ClBr\cdot{}^1/_3(C_6H_{12})$) C, H, N.

***N-tert*-Butyl-2-(3-azido-2-oxo-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (20b)** was prepared according to method A, using column chromatography on silica gel to separate the desired *cis* isomer: mp 167–170 °C; 38% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.24 (s, 9H), 2.74 (m, 1H), 2.88 (m, 1H), 3.00 (AB q, J_{AB} = 15, $\Delta\nu$ = 275, 2H), 3.87 (m, 1H), 4.14 (m, 1H), 6.9–7.4 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 28.6, 35.3, 48.6, 51.4, 54.3, 58.0, 126.0, 126.8, 126.9, 127.3, 127.5, 128.4, 128.6, 128.8, 128.9, 129.0, 129.1, 130.0, 130.1, 132.9, 139.6, 139.7, 140.3, 167.4, 169.5; IR (cm^{-1}, KBr) 2110 (N_3), 1660, 1700 (C=O); FAB MS (rel int) 426/428 (parent + 1, 100/36), 400 (35), 353 (87), 91 (50). Anal. ($C_{22}H_{24}N_5O_2Cl\cdot{}^1/_3H_2O$) C, H, N.

Method D. *N-tert*-Butyl-2-(3-amino-2-oxo-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)-ethanoic Acid Amide (21b). To a 25 mL round-bottomed flask equipped with N_2 inlet were added 255 mg (0.598 mmol) of **20b**, *cis* isomer, 5 mL of tetrahydrofuran, and 157 mg (0.598 mmol) of triphenylphosphine. The mixture was stirred to a solution, 0.4 mL water was added, and the reaction mixture was stirred for 18 h at room temperature. It was then partitioned between methylene chloride and 2 N hydrochloric acid, and the aqueous layer was separated and washed with fresh methylene chloride. The combined organic phase was washed with two portions of 2 N hydrochloric acid, and the combined aqueous extracts were adjusted to pH 12 with 6 N aqueous sodium hydroxide solution and then extracted with ethyl acetate. The organic phase was dried over sodium sulfate, evaporated, and chromatographed on silica gel using methylene chloride/methanol as eluant to afford 165 mg (65%) of a white foam: ^{1}H-NMR (δ, $CDCl_3$) 1.24 (s, 9H), 1.8–2.2 (m, 2H), 2.72 (m, 1H), 3.03 (AB q, J_{AB} = 15, $\Delta\nu$ = 264, 2H), 4.08 (m, 1H), 6.9–7.4 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 22.6, 28.6, 31.5, 44.4, 51.4, 54.1, 126.2, 126.5, 127.1, 128.4, 129.9, 132.5, 140.3, 140.6, 141.2, 167.9; IR (cm^{-1}, KBr) 1660, 1680 (C=O); FAB MS (rel int) 400 (parent, 100), 327 (75); HRMS calcd for $C_{22}H_{27}N_3O_2Cl$ 400.1786, found 400.179 52.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]-ethanoic acid amide (22b)** was prepared according to method A as the *cis* diastereomer: mp 234–236 °C; 83% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.27 (s, 9H), 2.8–3.0 (m, 2H), 3.24 (AB q, J_{AB} = 16, $\Delta\nu$ = 274, 2H), 4.21 (m, 1H), 4.55 (m, 1H), 5.76 (bs, 1H), 6.8–7.5 (m, 13H), 7.92 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 28.7, 36.6, 44.3, 50.3, 52.0, 53.1, 53.5, 117.0, 119.1, 122.4, 125.8, 126.2, 126.9, 128.5, 129.0, 129.6, 130.7, 133.2, 134.3, 139.6, 140.0, 140.5, 140.9, 155.0, 167.0, 173.0; IR (cm^{-1}, KBr) 1640 broad (C=O); FAB MS (rel int) 553/554/555/556/557/558 (parent, Cl^{35}/Cl^{37}, 75/32/54/19/10), 400 (100), 327 (82), 254 (83), 228 (73). Anal. ($C_{29}H_{30}N_4O_3Cl_2\cdot{}^1/_3H_2O$) C, H, N.

Preparation of *N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)-ureido)-2-oxo-5-(3-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (27). 5-(3-Chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (17c) was prepared according to method A: mp 174–176 °C; yield 51%; ^{1}H-NMR (δ, $CDCl_3$) 2.43 (m, 4H), 4.33 (m, 1H), 6.73 (d, J = 7, 1H), 6.9–7.3 (m, 7H), 8.90 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 32.7, 33.6, 44.8, 122.0, 125.7, 127.2, 127.3, 127.4, 127.6, 128.5, 129.0, 129.8, 134.5, 136.0, 137.4, 143.2, 175.3; IR (cm^{-1}, KBr) 1690 broad (C=O); FAB MS (rel int) 271/273 (parent, Cl^{35}/Cl^{37}, 91/30), 216/218 (Cl^{35}/Cl^{37}, 100/35), 180 (34). Anal. ($C_{16}H_{14}NOCl$) C, H, N.

3-Bromo-5-(3-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (23) was prepared according to method A as a mixture of diastereomers: mp 154–158 °C; 51% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.8–3.2 (multiplets, 2H), 4.45 (m, 1H), 4.60 (dd, J = 8, 12) and 4.75 (m, 1H), (m, 2H), 6.7–7.4 (m, 8H), 8.46 and 8.70 (bs's, 1H); ^{13}C-NMR (δ, $CDCl_3$) 26.9, 43.3, 44.5, 44.7, 44.8, 45.7, 46.6, 122.4, 122.5, 122.6, 126.2, 126.4, 126.7, 127.1, 127.2, 127.4, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.8, 129.0, 129.2, 130.1, 134.6, 134.8, 135.2, 135.3, 136.1, 141.3, 142.5, 168.8, 169.7; IR (cm^{-1}, KBr) 1690 (C=O); EI MS (rel int) 351 (parent, 100), 270 (53), 242 (48). Anal. ($C_{16}H_{13}NOBrCl$) H, N; C: Δ 0.67.

***N-tert*-Butyl-2-[3-bromo-2-oxo-5-(3-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (24)** was prepared according to method A: mp 148–152 °C (from cyclohexane); 57% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.30 (s, 9H), 2.8–3.0 (m, 2H), 4.32 (m, 2H), 4.51 (dd, J = 8, 12, 1H), 4.72 (m, 1H), 5.88 (bs, 1H), 6.61 (d, J = 7, 1H), 7.0–7.4 (m, 7H); IR (cm^{-1}, KBr) 1630, 1680 (C=O); FAB MS (rel int) 464 (parent, 10), 383 (20), 356 (70), 310 (100), 284 (97), 165 (46), 57 (93). Anal. ($C_{22}H_{24}N_2O_2BrCl\cdot{}^1/_2(C_6H_{12})$) C, H, N.

***N-tert*-Butyl-2-[3-azido-2-oxo-5-(3-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (25)** was prepared according to method A, using column chromatography on silica gel with hexane/ethyl acetate to separate the diastereomers, with the more polar, *cis* isomer giving mp 132–135 °C: 72.5% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.28 (s, 9H), 2.80 (m, 2H), 3.13 (AB q, J_{AB} = 15, $\Delta\nu$ = 288, 2H), 3.95 (m, 1H), 4.15 (m, 1H), 6.04 (bs, 1H), 6.8–7.5 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 28.6, 35.9, 43.6, 51.4, 54.5, 58.1, 124.0, 125.9, 126.7, 126.8, 126.9, 127.0, 127.8, 127.9, 129.6, 129.7, 129.9, 130.3, 134.5, 136.9, 141.0, 143.4, 167.6, 169.6; IR (cm^{-1}, KBr) 2110 (N_3), 1660 broad (C=O); FAB MS (rel int) 426/428 (parent, Cl^{35}/Cl^{37}, 86/32), 400/402 (Cl^{35}/Cl^{37}, 72/26), 353/355 (Cl^{35}/Cl^{37}, 100/37), 327 (44), 228 (45). Anal. ($C_{22}H_{24}N_5O_2Cl$) C, H, N.

***N-tert*-Butyl-2-[3-amino-2-oxo-5-(3-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (26)** was prepared by method D as a foam in 95% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.26 (s, 9H), 2.32 (bs, 2H), 2.49 (m, 1H), 2.72 (m, 1H), 3.14 (AB q, J_{AB} = 15, $\Delta\nu$ = 275, 2H), 3.52 (m, 1H), 4.09 (m, 1H), 6.00 (bs, 1H), 6.9–7.4 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 22.6, 28.6, 31.5, 44.4, 51.4, 54.1, 124.3, 125.6, 126.5, 126.8, 127.4, 129.1, 129.5, 130.2, 134.2, 141.6, 144.4, 168.0, 1 carbonyl carbon not visible in this scan; IR (cm^{-1}, KBr) 1660, 1680 broad (C=O); FAB MS (rel int) 400/402 (parent, Cl^{35}/Cl^{37}, 100/36), 327/329 (Cl^{35}/Cl^{37}, 78/27), 271 (27); HRMS calcd for $C_{22}H_{27}N_3O_2Cl$ 400.1786, found 400/178 76.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-(3-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (27)** was prepared according to method A: mp 240–243 °C; 84% yield; ^{1}H-NMR (δ, $CDCl_3$, TFA) 1.33 (s, 9H), 2.79 (m, 1H), 3.02 (m, 1H), 3.34 (AB q, J_{AB} = 16, $\Delta\nu$ = 143, 2H), 4.25 (m, 1H), 4.59 (m, 1H), 6.7–7.5 (m, 15H); ^{13}C-NMR (δ, $CDCl_3$, TFA) 27.8, 36.6, 43.3, 44.0, 50.3, 53.4, 53.5, 121.2, 123.4, 124.2, 124.7, 126.0, 126.8, 127.2, 129.5, 129.9, 130.0, 130.7, 131.1, 134.8, 135.5, 136.4, 137.2, 139.2, 142.7, 157.3, 169.1, 173.9; IR (cm^{-1}, KBr) 1640 broad (C=O); FAB MS (rel int) 553/554/555/556/557 (parent + 1, Cl^{35}/Cl^{37}, 14/6/12/3/2), 309 (16), 155 (60), 135 (30), 119 (100), 103 (42). Anal. ($C_{29}H_{30}N_4O_3Cl_2\cdot{}^1/_3H_2O$) C, H, N.

Method E. 4-Phenyl-8-methyl-1,2,3,4-tetrahydronaphth-1-one (28) and 4-Phenyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one (29a). 8-Methyl-1-naphthol (7.4 g, 46.83 mmol) was taken up in 50 mL of dry benzene to which was added 13.08 g (98.35 mmol) of aluminum chloride, and the reaction mixture was heated to 60 °C for 2 h (product shows R_f = 0.5 in 8:1 hexane:ethyl acetate). The reaction was cooled, poured over ice:water, and extracted into ethyl acetate, and the organic layer was washed with brine, dried over sodium sulfate, and evaporated. The products were separated by chromatography on silica gel using hexane:ethyl acetate as eluant and crystallized separately from methanol. X-ray

analysis of single crystals of both compounds, grown in methanol, established the structures of the two isomers.

8-Methyl isomer (28): mp 60–63 °C; 24% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.2–2.7 (m, 4H), 2.68 (s, 3H), 4.28 (m, 1H), 6.8–7.3 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 23.4, 31.2, 38.1, 46.1, 126.6, 126.8, 127.8, 128.6, 131.0, 131.6, 132.4, 141.2, 144.1, 147.3, 200.0; IR (cm^{-1}, KBr) 1680 (C=O); MS (rel int) 236 (parent, 100), 208 (85), 165 (50). Anal. ($C_{17}H_{16}O$) C, H, N.

Single-Crystal X-ray Analysis of 28. A representative crystal was surveyed and a 1 Å data set (maximum sin λ/ν = 0.5) was collected on a Siemens R3RA/v diffractometer. Atomic scattering factors were taken from ref 36. All crystallographic calculations were facilitated by the SHELXTL[37] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table C1 (supplementary material). A trial structure was obtained by direct methods. This trial structure was refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogen on nitrogen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R index was 10.61%. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package. Coordinates, anisotropic temperature factors, distances and angles are available as supplementary material (Tables C2–C6).

7-Methyl isomer (29a): mp 72–74 °C; 50% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.27 (m, 1H), 2.36 (s, 3H), 2.43 (m, 1H), 2.59 (m, 1H), 2.66 (m, 1H), 4.24 (m, 1H), 6.85 (d, J = 8, 1H), 7.10 (m, 2H), 7.2–7.4 (m, 4H), 7.90 (d, J = 1, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 32.0, 36.8, 45.0, 126.7, 126.9, 127.2, 128.4, 128.6, 129.5, 132.6, 134.6, 143.5, 143.9, 198.4; IR (cm^{-1}, KBr) 1681 (C=O); MS (rel int) 236 (parent, 100), 194 (70), 165 (50). Anal. ($C_{17}H_{16}O$) C, H, N.

Single-Crystal X-ray Analysis of 29a. A representative crystal was surveyed and a 1 Å data set (maximum sin λ/ν = 0.5) was collected on a Siemens R3RA/v diffractometer. Atomic scattering factors were taken from ref 36. All crystallographic calculations were facilitated by the SHELXTL[37] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table B1 (supplementary material). A trial structure was obtained by direct methods. This trial structure was refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogen on nitrogen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R index was 5.38%. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package. Coordinates, anisotropic temperature factors, distances and angles are available as supplementary material (Tables B2–B6).

Preparation of *N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)-ureido)-2-oxo-5-phenyl-9-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (38). 4-Phenyl-8-methyl-1,2,3,4-tetrahydronaphth-1-one oxime (30) was prepared according to method C: mp 130–136 °C; 73% yield from tetralone **28**; ^{1}H-NMR (δ, $CDCl_3$) 2.10 (m, 2H), 2.65 (s, 3H), 2.7–2.9 (m, 2H), 4.07 (m, 1H), 6.79 (d, J = 7, 1H), 7.1–7.4 (m, 7H), 9.18 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 22.9, 23.3, 28.6, 46.1, 126.2, 126.5, 128.3, 128.5, 130.1, 130.5, 137.0, 143.3, 143.8, 156.9; FAB MS (rel int) 251 (parent, 100), 234 (70), 130 (30). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.19; H, 6.61; N, 5.51.

5-Phenyl-9-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (32) was prepared according to method C: mp 154–157 °C; 81% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.35 (s, 3H), 2.4–2.6 (m, 4H), 4.38 (m, 1H), 6.59 (d, J = 8, 1H), 6.93 (t, J = 7, 1H), 7.07 (m, 1H), 7.2–7.4 (m, 5H), 8.62 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 18.1, 32.7, 33.8, 44.9, 125.6, 126.0, 127.0, 128.5, 128.8, 129.0, 130.4, 136.0, 137.6, 141.2, 175.4; IR (cm^{-1}, KBr) 1680 (C=O); EI MS (rel int) 251 (parent, 100), 196 (80). Anal. ($C_{17}H_{17}NO$) C, H, N.

3-Bromo-5-phenyl-9-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (34) was prepared according to method A as a mixture of diastereomers, one of which was separated by crystallization to give mp 240–243 °C, in 44% yield: ^{1}H-NMR (δ, $CDCl_3$) 2.33 (s, 3H), 2.89 (m, 1H), 3.10 (m, 1H), 4.45 (m, 1H), 4.58 (dd, J = 7, 12, 1H), 6.57 (d, J = 8, 1H), 6.97 (t, J = 8, 1H), 7.09 (d, J = 8, 1H), 7.2–7.4 (m, 5H), 8.28 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 18.1, 45.1, 45.9, 46.9, 126.0, 126.6, 127.5, 128.8, 128.9, 129.0, 129.2, 129.3, 129.4, 130.9, 134.6, 136.6, 139.4, 168.9; IR (cm^{-1}, KBr) 1680 (C=O); EI MS (rel int) 329/331 (parent, Br^{79}/Br^{81}, 92/90), 250 (100), 222 (95), 194 (72). Anal. ($C_{17}H_{16}NOBr$) C, H, N.

The remaining material, 26% yield, was obtained as a mixture of diastereomers and was combined with the above diastereomer in the next step.

***N-tert*-Butyl-2-(3-bromo-2-oxo-5-phenyl-9-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (*cis* and *trans* isomers 35c and 35t)** were prepared according to method A. The diastereomers were separated by chromatography on silica gel using hexane/ethyl acetate as eluant and then crystallized from methylene chloride/hexane.

***Cis* isomer, 35c**: mp 199–202 °C; 15% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.35 (s, 9H), 2.26 (s, 3H), 2.71 (t, J = 14, 1H), 3.12 (m, 1H), 4.15 (AB q, J_{AB} = 14.5, $\Delta\nu$ = 256, 2H), 4.62 (d, J = 9, 1H), 5.15 (dd, J = 5, 14, 1H), 6.01 (bs, 1H), 6.48 (d, J = 7, 1H), 7.0–7.1 (m, 2H), 7.2–7.4 (m, 5H); ^{13}C-NMR (δ, $CDCl_3$) 19.0, 28.8, 41.8, 43.3, 51.5, 55.1, 126.3, 127.1, 127.7, 128.6, 128.8, 130.1, 132.6, 139.6, 140.3, 140.4, 166.8, 170.0; IR (cm^{-1}, KBr) 1640, 1690 (C=O); FAB MS (rel int) 442/444 (parent + 1, Br^{79}/Br^{81}, 20/19), 336 (63), 290 (100), 263 (84), 235 (50), 57 (68). Anal. ($C_{23}H_{27}N_2O_2Br$) C, H, N.

***Trans* isomer 35t**: mp 227–230 °C; 63% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.33 (s, 9H), 2.27 (s, 3H), 2.7–2.9 (m, 2H), 4.16 (AB q, J_{AB} = 14, $\Delta\nu$ = 254, 2H), 4.48 (dd, J = 8, 12, 1H), 4.95 (m, 1H), 6.25 (bs, 1H), 6.48 (d, J = 7, 1H), 7.0–7.4 (m, 7H); ^{13}C-NMR (δ, $CDCl_3$) 18.7, 28.7, 43.5, 45.0, 46.8, 51.5, 54.7, 125.5, 127.2, 128.2, 128.6, 128.8, 130.4, 132.3, 139.4, 139.5, 166.8, 169.2; IR (cm^{-1}, KBr) 1660, 1700 broad (C=O); FAB MS (rel int) 442/444 (parent + 1, Br^{79}/Br^{81}, 42/43), 336 (65), 290 (69), 263 (100), 235 (60), 57 (37); HRMS calcd for $C_{23}H_{27}N_2O_2Br$ 442.1249, found 442.126 01. Anal. ($C_{23}H_{27}N_2O_2Br$) H, N; C: calcd 62.31, found 62.83.

Single-Crystal X-ray Analysis of 35t. A representative crystal was surveyed and a 1 Å data set (maximum sin λ/ν = 0.5) was collected on a Siemens R3RA/v diffractometer. Atomic scattering factors were taken from ref 36. All crystallographic calculations were facilitated by the SHELXTL[37] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table D1 (supplementary material). A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogen on nitrogen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R index was 4.35%. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package. Coordinates, anisotropic temperature factors, distances and angles are available as supplementary material (Tables D2–D6).

***N-tert*-Butyl-2-(3-azido-2-oxo-5-phenyl-9-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (36)** was prepared according to method A from the *trans* isomer in the preceding step as a mixture of diastereomers, which were separated by chromatography on silica gel using hexane:ethyl acetate as eluant. The desired *cis* isomer gave mp 160–164 °C, 76% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.35 (s, 9H), 2.33 (s, 3H), 2.4 and 2.7–2.9 (m's, 2H), 3.8 and 4.5 (m's, 3H), 4.9–5.1 (m, 1H), 6.04 (bs, 1H), 6.5 and 7.0–7.4 (m's, 8H); IR

(cm^{-1}, KBr) 2110 (N_3), 1680 broad (C=O); FAB MS (rel int) 406 (parent + 1, 100), 380 (37), 333 (90). Anal. ($C_{23}H_{27}N_5O_2$) C, H, N.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-phenyl-9-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (37)** was prepared according to method A as an oil in 13% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.23 (s, 9H), 2.20 (s, 3H), 2.57 (m, 2H), 2.58 (AB q, J_{AB} = 16, $\Delta\nu$ = 228, 2H), 3.4 (m, 1H), 4.12 (m, 1H), 7.0–7.3 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 18.5, 28.4, 28.6, 38.1, 44.5, 50.0, 50.4, 50.9, 56.0, 126.2, 126.6, 128.1, 128.3, 128.5, 131.2, 135.8, 139.7, 140.0, 141.1, 169.0, 176.8; IR (cm^{-1}, KBr) 1680 broad (C=O); FAB MS (rel int) 380 (parent + 1, 100), 307 (100), 251 (43), 208 (44). HRMS calcd for $C_{23}H_{27}N_5O_2$ 380.2331, found 380.234 62.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-9-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (38)** was prepared according to method A: mp 260–262 °C; 77% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.20 (s, 9H), 2.30 (s, 3H), 2.80 (AB q, J_{AB} = 16, $\Delta\nu$ = 98, 2H), 2.8–3.0 (m, 2H), 4.26 (m, 1H), 4.48 (m, 1H), 6.17 (bs, 1H), 6.8–7.3 (m, 12H), 7.56 (bs, 1H), 7.96 (m, 1H); ^{13}C-NMR (δ, $CDCl_3$) 18.9, 28.5, 35.6, 44.7, 50.2, 51.5, 54.4, 117.1, 119.2, 122.4, 126.4, 126.7, 128.4, 128.5, 128.8, 129.7, 131.7, 134.4, 135.6, 139.3, 139.8, 140.6, 141.3, 155.1, 167.4, 174.7; IR (cm^{-1}, KBr) 1640 broad (C=O); FAB MS (rel int) 533/535 (parent, Cl^{35}/Cl^{37}, 23/8), 460 (100), 408 (68), 234 (85), 208 (75). Anal. ($C_{31}H_{36}N_4O_3Cl$) C, H, N.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (43a). 4-Phenyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one oxime (31a)** was prepared according to method C: mp 143–146 °C; yield 72%; ^{1}H-NMR (δ, $CDCl_3$) 2.0–2.2 (m, 2H), 2.37 (s, 3H), 2.85 (t, J = 7, 2H), 4.13 (dd, J = 4, 7, 1H), 6.85 (d, J = 8, 1H), 7.0–7.4 (m, 6H), 7.83 (bs, 1H), 9.50 (m, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.2, 21.4, 29.7, 44.8, 124.3, 124.4, 126.4, 128.5, 128.8, 129.3, 130.5, 130.6, 136.5, 138.8, 144.1, 155.5; MS (rel int) 251 (parent, 100), 234 (45), 83 (42). Anal. ($C_{17}H_{17}NO$) C, H, N.

5-Phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (33a) was prepared according to method C: mp 230–234 °C; yield 28.5%; ^{1}H-NMR (δ, $CDCl_3$) 2.21 (s, 3H), 2.3–2.5 (m, 4H), 4.25 (dd, J = 7, 11, 1H), 6.52 (m, 1H), 6.73 (m, 2H), 7.1–7.3 (m, 5H); ^{13}C-NMR (δ, $CDCl_3$) 20.7, 32.7, 33.8, 44.7, 122.4, 126.4, 126.9, 128.5, 128.8, 133.7, 136.9, 137.2, 141.1, 176.0; IR (cm^{-1}, KBr) 1670 (C=O); MS (rel int) 251 (parent, 96), 196 (100). Anal. ($C_{17}H_{17}NO$) C, H, N.

3-Bromo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (39a) was prepared according to method A: mp 228–232 °C; 46% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.23 (s, 3H), 2.64 (m, 1H), 2.98 (m, 1H), 4.27 (m, 1H), 4.57 (dd, J = 8, 12, 1H), 6.55 (d, J = 8, 1H), 6.8 (m, 2H), 7.1–7.3 (m, 5H); ^{13}C-NMR (δ, $CDCl_3$) 20.7, 44.7, 46.1, 47.2, 123.0, 127.2, 127.4, 128.2, 128.7, 128.8, 132.9, 135.8, 137.7, 139.4, 169.2; IR (cm^{-1}, KBr) 1680 (C=O); MS (rel int) 329/331 (parent, Br^{79}/Br^{81}, 53/49), 250 (100), 222 (68), 194 (40), 91 (42). Anal. ($C_{17}H_{16}NOBr\cdot{}^1/_4H_2O$) C, H, N.

***N-tert*-Butyl-2-(3-bromo-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (40a)** was prepared according to method A: mp 227–230 °C; 36% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.34 (s, 9H), 2.28 (s, 3H), 2.79 (m, 1H), 2.95 (m, 1H), 4.35 (m, 2H), 4.56 (m, 2H), 6.14 (bs, 1H), 6.54 (d, J = 8, 1H), 6.87 (d, J = 8, 1H), 7.11 (bs, 1H), 7.2–7.4 (m, 5H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 28.8, 43.7, 45.7, 47.3, 51.5, 54.8, 123.7, 127.3, 127.6, 128.2, 128.7, 128.8, 134.6, 138.0, 139.3, 140.7, 167.0, 168.2; IR (cm^{-1}, KBr) 3330 (NH), 1660 (C=O); MS (rel int) 443/445 (parent, Br^{79}/Br^{81}, 58/60), 370/372, Br^{79}/Br^{81}, 100/97), 292 (65), 262 (85), 119 (68); HRMS calcd for $C_{23}H_{27}N_2O_2Br$ 442.1249, found 442.123 21.

***N-tert*-Butyl-2-(3-azido-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (41a)** was prepared according to method A: mp 112–115 °C; 56% yield of the *cis* isomer after separation by column chromatography; ^{1}H-NMR (δ, $CDCl_3$) 1.28 (s, 9H), 2.33 (s, 3H), 2.72 (m, 1H), 2.90 (m, 1H), 3.04 (AB q, J_{AB} = 15, $\Delta\nu$ = 275, 2H), 3.92 (m, 1H), 4.15 (m, 1H), 6.10 (bs, 1H), 6.9–7.4 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 21.1, 28.6, 35.6, 43.3, 51.3, 54.6, 58.3, 126.1, 126.2, 126.3, 126.4, 126.5, 128.4, 128.6, 130.1, 130.2, 134.9, 139.3, 140.8, 141.3, 167.9, 170.0; IR (cm^{-1}, KBr) 1670, 1700 (C=O); MS (rel int) 406 (parent, 100), 380 (45), 333 (94), 208 (43). Anal. ($C_{23}H_{27}N_5O_2$) C, H, N.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (42a)** was prepared according to method A: mp 170–180 °C; 75% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.26 (s, 9H), 2.27 (s, 3H), 3.03 (AB q, J_{AB} = 16, $\Delta\nu$ = 333, 2H), 3.05 (m, 1H), 3.22 (m, 1H), 4.12 (m, 2H), 6.29 (bs, 1H), 7.0–7.3 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 21.1, 26.9, 28.7, 34.4, 43.3, 50.4, 51.7, 53.4, 125.7, 126.4, 128.4, 128.6, 128.7, 130.5, 130.6, 135.0, 139.2, 140.0, 141.1, 167.8, 169.2; IR (cm^{-1}, KBr) 1680 broad (C=O); FAB MS (rel int) 380 (parent + 1, 100), 307 (92), 251 (37), 208 (36); HRMS calcd for $C_{23}H_{29}N_3O_2$ 379.2253, found 379.2267.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (43a)** was prepared according to method A: mp 155–165 °C; 68% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.29 (s, 9H), 2.33 (s, 3H), 2.8–3.0 (m, 2H), 3.32 (AB q, J_{AB} = 16, $\Delta\nu$ = 285, 2H), 4.20 (m, 1H), 4.56 (m, 1H), 6.6–7.3 (m, 13H), 7.56 (bs, 1H), 8.00 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.1, 28.7, 36.8, 44.0, 50.5, 51.9, 53.1, 60.4, 116.9, 118.9, 122.0, 124.8, 126.3, 126.4, 126.5, 128.3, 128.4, 129.5, 130.7, 134.2, 135.0, 139.1, 140.7, 140.8, 142.0, 155.2, 167.4, 173.4; IR (cm^{-1}, KBr) 1640 broad (C=O); FAB MS (rel int) 533/535 (parent + 1), Cl^{35}/Cl^{37}, 69/26), 460 (100), 307 (52), 234 (60), 208 (70). Anal. ($C_{30}H_{33}N_4O_3Cl$) C, H, N.

Method F: Improved Procedure for the Preparation of 4-Phenyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one (29a). 1-Acetoxy-7-methylnaphthalene (44a). To a 2 L round-bottomed flask equipped with condenser and N_2 inlet were added 88.3 g (0.552 mol) of 7-methyl-1,2,3,4-tetrahydronaphth-1-one, 851 mL (7.73 mol) of isopropenyl acetate, and 1.8 g of *p*-toluenesulfonic acid. The reaction mixture was refluxed 14 h and cooled in an ice bath, 250 g (1.104 mol) of DDQ was added in three portions over 10 min (exotherm controlled by ice bath), and the reaction mixture was heated to 80–90 °C for 1.5 h. The reaction mixture was cooled and the hydroquinone byproduct from the DDQ filtered. The filtrate was evaporated, adsorbed onto silica gel, and then chromatographed using 85:15 hexane:ethyl acetate to afford 82 g (74% for three steps) of a red oil: ^{1}H-NMR (δ, $CDCl_3$) 2.46 (s, 3H), 2.54 (s, 3H), 7.2–7.4 and 7.6–7.8 (m, 6H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 22.0, 118.2, 120.0, 124.5, 125.8, 127.0, 128.0, 128.8, 133.1, 136.3, 146.2, 169.5.

7-Methyl-1-naphthol (45a). To a 250 mL round-bottomed flask equipped with condenser and N_2 inlet were added 60 mL of ethanol and 8.28 g (148 mmol) of powdered potassium hydroxide. After cooling, a solution of 8.0 g (40 mmol) of **44a** in 50 mL of ethanol was added, and the reaction mixture was stirred at room temperature for 1.2 h. The reaction mixture was evaporated to a small volume, taken up in methylene chloride:water, and separated, and the aqueous layer was washed again with methylene chloride. The aqueous layer was adjusted to pH 1 with 6 N hydrochloric acid and extracted into ethyl acetate, and the organic layer was washed with brine, dried over sodium sulfate, and evaporated to a tan solid: ^{1}H-NMR (δ, $CDCl_3$) 2.52 (s, 3H), 6.80 (m, 1H), 7.2–7.4 (m, 3H), 7.71 (m, 1H), 7.98 (d, J = 1, 1H); MS (rel int) 158 (100, parent), 129 (23), 115 (18).

4-Phenyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one (29a). The above solid was taken up in 100 mL of dry benzene and treated according to method D to give the product as an oil in 78% yield. Spectral data matched that of a sample prepared by method E.

Preparation of *N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-8-ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (43b). 7-Ethyl-1-acetoxynaphthalene (44b) was prepared according to method F from 7-ethyl-1,2,3,4-tetrahydronaphth-1-one in 52% yield as an oil: ^{1}H-NMR (δ, $CDCl_3$) 1.32 (t, J = 7, 3H), 2.47 (s, 3H), 2.82 (q, J = 7, 2H), 6.89 (m, 1H), 7.12 (m, 1H), 7.39 (m, 2H), 7.6–7.8 (m, 3H); MS (rel int) 214 (parent, 38), 172 (100), 157 (39), 43 (30); IR (cm^{-1}, KBr) 1767 (C=O). This oil was

converted to the phenol **45b** as in method F and used directly in the next step.

4-Phenyl-7-ethyl-1,2,3,4-tetrahydronaphth-1-one (29b) was prepared according to method E in 41% yield as an oil: ^{1}H-NMR (δ, $CDCl_3$) 1.24 (t, J = 7, 3H), 2.29 (m, 1H), 2.46 (m, 1H), 2.6–2.8 (m, 2H), 2.66 (q, J = 7, 2H), 4.25 (dd, J = 4, 8, 1H), 6.9–7.4 (m, 7H), 7.94 (m, 1H); ^{13}C-NMR (δ, $CDCl_3$) 15.4, 27.0, 28.4, 32.0, 36.9, 45.1, 126.0, 126.8, 128.6, 129.6, 132.7, 133.5, 143.1, 143.9, 198.3; IR (cm^{-1}, KBr) 1682 (C=O); MS (rel int) 250 (parent, 100), 221 (60), 208 (70); HRMS calcd for $C_{18}H_{18}O$ 250.1353, found 250.133 37.

4-Phenyl-7-ethyl-1,2,3,4-tetrahydronaphth-1-one oxime (31b) was prepared according to method C: mp 120–122 °C; yield 100%; ^{1}H-NMR (δ, $CDCl_3$) 1.23 (t, J = 8, 3H), 2.10 (m, 1H), 2.19 (m, 1H), 2.63 (q, J = 8, 2H), 2.79 (t, J = 7, 2H), 4.10 (dd, J = 4, 7, 1H), 6.9–7.4 (m, 7H), 7.81 (bs, 1H), 8.42 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 15.5, 21.2, 28.6, 29.6, 44.8, 123.1, 126.4, 128.4, 128.5, 129.3, 130.6, 139.0, 142.8, 144.1, 155.6; MS (rel int) 265 (parent, 100), 236 (60). Anal. ($C_{18}H_{19}NO$) C, H, N.

Method G. Preparation of 5-Phenyl-8-ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (33b). To a 250 mL round-bottomed flask equipped with condenser and N_2 inlet were added 3.29 g (12.41 mmol) of **31b** and 83 mL of 1,2-dichloroethane to give a solution. To the solution was added 33 g of ethyl polyphosphate (PPE), and the flask was plunged into a 90 °C oil bath. After being stirred for 30 min, the reaction mixture was cooled, water was added dropwise with caution, and stirring was continued overnight. The layers were separated, and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with water and brine, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography on silica using methylene chloride/ethyl acetate as eluant to afford 2.171 g (66%) of a white solid after slurrying with hexane: mp 190–193 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.20 (t, J = 8, 3H), 2.4–2.6 (m, 6H), 4.37 (m, 1H), 6.67 (d, J = 8, 1H), 6.85 (d, J = 8, 1H), 6.91 (bs, 1H), 7.2–7.4 (m, 5H), 8.97 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 15.4, 28.2, 32.9, 33.9, 44.8, 121.4, 125.0, 127.0, 128.6, 128.9, 134.0, 137.3, 141.3, 143.6, 175.8; IR (cm^{-1}, KBr) 1665 (C=O); MS (rel int) 265 (parent, 95), 210 (100). Anal. ($C_{18}H_{19}NO$) C, H, N.

3-Bromo-5-phenyl-8-ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (39b) was prepared according to method A: mp 231–235 °C; 76% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.14 (t, J = 7, 3H), 2.53 (q, J = 7, 2H), 2.83 (m, 1H), 2.90 (bs, 1H), 3.07 (m, 1H), 4.37 (m, 1H), 4.57 (dd, J = 8, 12, 1H), 6.58 (d, J = 8, 1H), 6.86 (m, 2H), 7.2–7.4 (m, 5H); ^{13}C NMR (δ, $CDCl_3$) 15.2, 28.1, 43.6, 44.8, 45.5, 46.1, 47.2, 121.8, 125.6, 126.0, 127.0, 127.4, 128.0, 128.2, 128.7, 128.8, 133.1, 135.8, 136.0, 139.4, 144.1, 169.1; IR (cm^{-1}, KBr) 1680 (C=O); MS (rel int) 346/348 (parent, Br^{79}/Br^{81}, 100/95), 264 (45), 155 (40), 119 (85). Anal. ($C_{18}H_{18}NOBr$) C, H, N.

***N-tert*-Butyl-2-(3-bromo-2-oxo-5-phenyl-8-ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (40b)** was prepared according to method A: mp 211–213 °C; 66% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.18 (t, J = 7, 3H), 1.34 (s, 9H), 2.59 (q, J = 7, 2H), 2.81 (m, 1H), 2.98 (m, 1H), 4.36 (m, 2H), 4.58 (m, 2H), 6.09 (bs, 1H), 6.58 (d, J = 8, 1H), 6.90 (m, 1H), 7.12 (bs, 1H), 7.2–7.4 (m, 5H); ^{13}C-NMR (δ, $CDCl_3$) 15.3, 28.3, 28.7, 43.8, 45.7, 47.2, 51.5, 55.0, 122.5, 127.0, 127.3, 127.7, 128.7, 128.8, 134.8, 139.3, 140.8, 144.4, 167.1, 168.3; IR (cm^{-1}, KBr) 1660 broad (C=O); MS (rel int) 457/459 (parent, Br^{79}/Br^{81}, 52/54), 384/386 (Br^{79}/Br^{81}, 98/100), 304 (70), 276 (94). Anal. ($C_{24}H_{29}N_2O_2Br$) C, H, N.

***N-tert*-Butyl-2-(3-azido-2-oxo-5-phenyl-8-ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (41b)** was prepared according to method A: mp 124–127 °C; 73% yield of the *cis* isomer; ^{1}H-NMR (δ, $CDCl_3$) 1.22 (t, J = 7, 3H), 1.29 (s, 9H), 2.64 (q, J = 7, 2H), 2.74 (m, 1H), 2.90 (m, 1H), 3.06 (AB q, J_{AB} = 16, $\Delta\nu$ = 291, 2H), 3.95 (m, 1H), 4.18 (m, 1H), 6.9–7.4 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 15.2 28.4, 28.6, 35.6, 43.3, 51.3, 54.6, 58.3, 125.1, 126.1, 126.5, 127.1, 128.5, 130.2, 135.1, 140.9, 141.3, 145.6, 167.9, 170.0; IR (cm^{-1}, KBr) 2110 (N_3), 1660, 1680 (C=O); MS (rel int) 420 (parent + 1, 100), 394 (40), 347 (97), 222 (49). Anal. ($C_{24}H_{29}N_5O_2$) C, H, N.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-phenyl-8-ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (42b)** was prepared according to method A: mp 68–78 °C; 100% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.21 (t, J = 7, 3H), 1.29 (s, 9H), 2.4–2.8 and 3.4–3.6 (m's, 5H), 2.62 (q, J = 7, 2H), 4.10 (m, 1H), 6.9–7.4 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 15.2, 28.3, 28.6, 31.6, 39.2, 44.0, 51.3, 54.2, 124.7, 126.2, 126.3, 126.7, 128.3, 130.1, 135.8, 141.3, 142.1, 145.1, 168.2, 174.6; IR (cm^{-1}, KBr) 1670 broad (C=O); MS (rel int) 394 (parent + 1, 93), 321 (100), 265 (58), 222 (59); HRMS calcd for $C_{24}H_{31}N_3O_2$ 393.2409, found 393.245 13.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-8-ethyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]-ethanoic acid amide (43b)** was prepared according to method A in 93% yield: mp 145–150 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.24 (t, J = 7, 3H), 1.31 (s, 9H), 2.65 (q, J = 7, 2H), 2.95 (m, 2H), 3.35 (AB q, J_{AB} = 16, $\Delta\nu$ = 295, 2H), 4.27 (m, 1H), 4.62 (m, 1H), 6.6–7.4 (m, 13H), 7.56 (bs, 1H), 7.94 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 15.0, 28.4, 28.7, 36.9, 44.1, 50.5, 51.9, 53.1, 116.9, 119.0, 122.1, 123.5, 126.3, 126.5, 127.2, 128.3, 129.5, 130.8, 134.3, 135.2, 140.7, 140.8, 142.0, 145.3, 155.2, 167.4, 173.5; IR (cm^{-1}, KBR) 1640, 1660 (C=O); FAB MS (rel int) 547 (parent, 55), 474 (98), 321 (65), 248 (88), 222 (100). Anal. ($C_{31}H_{35}ClN_4O_3 \cdot {}^1/_4H_2O$) C, H, N.

Preparation of *N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)-ureido)-2-oxo-5-phenyl-8-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (43c). 7-Chloro-1-acetoxynaphthalene (44c) was prepared according to method F from 7-chloro-1,2,3,4-tetrahydronaphth-1-one as an oil in 78% yield: ^{1}H-NMR (δ, $CDCl_3$) 2.48 (s, 3H), 7.2–7.8 (m's, 6H); IR (cm^{-1}, KBr) 1767 (C=O); EI MS (rel int) 220/222 (parent, Cl^{35}/Cl^{37}, 65/25), 180 (98), 178 (100), 115 (87), 43 (69); HRMS calcd for $C_{12}H_9O_2Cl^{35}$ 220.0288, found 220.029 26.

This oil was converted to the phenol **45c** as in method F and used directly in the next step.

4-Phenyl-7-chloro-1,2,3,4-tetrahydronaphth-1-one (29c) was prepared according to method C in 41% yield as an oil: ^{1}H-NMR (δ, $CDCl_3$) 2.2–2.8 (m, 4H), 4.27 (m, 1H), 6.9–7.4 (m, 7H), 8.05 (d, J = 2, 1H); ^{13}C-NMR (δ, $CDCl_3$) 31.7, 36.6, 44.9, 126.8, 126.9, 127.1, 128.5, 128.8, 131.3, 133.4, 133.5, 143.2, 144.6, 196.7; IR (cm^{-1}, KBr) 1682 (C=O); EI MS (rel int) 256/258 (parent, Cl^{35}/Cl^{37}, 97/35), 193 (100), 165 (90).

4-Phenyl-7-chloro-1,2,3,4-tetrahydronaphth-1-one oxime (31c) was prepared according to method C: mp 120–122 °C; yield 100%; ^{1}H-NMR (δ, $CDCl_3$) 2.0–2.2 (m, 2H), 2.84 (t, J = 7, 2H), 4.11 (m, 1H), 4.27 (m, 1H), 6.87 (d, J = 8, 1H), 7.0–7.4 (m, 7H), 8.01 (d, J = 3, 1H), 9.40 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.3, 29.4, 44.7, 123.9, 126.7, 128.5, 128.7, 129.5, 130.8, 132.3, 132.9, 140.1, 143.4, 154.7; EI MS (rel int) 271/273 (parent, Cl^{35}/Cl^{37}, 100/33), 91 (28).

5-Phenyl-8-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (33c) was prepared according to method G: mp 190–193 °C; yield 66%; ^{1}H-NMR (δ, $CDCl_3$) 2.4–2.5 (m, 4H), 4.29 (m, 1H), 6.66 (d, J = 8, 1H), 6.9–7.4 (m, 7H); ^{13}C-NMR (δ, $CDCl_3$) 32.7, 33.4, 44.7, 121.8, 125.6, 127.3, 128.7, 128.8, 130.0, 132.7, 135.4, 138.2, 140.4, 175.1; IR (cm^{-1}, KBr) 1680 (C=O); EI MS (rel int) 271/273 (parent, Cl^{35}/Cl^{37}, 30/10), 216 (100), 180 (30).

3-Bromo-5-phenyl-8-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (39c) was prepared according to method A as a mixture of diastereomers: mp 201–215 °C; 53% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.85 (m, 1H), 3.08 (m, 1H), 4.38 (m, 1H), 4.57 (m, 1H), 6.6 and 7.0–7.4 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) (major diastereomer) 44.8, 45.7, 46.7, 122.4, 126.4, 127.7, 128.8, 128.9, 129.7, 133.2, 134.5, 137.2, 138.8, 169.0; IR (cm^{-1}, KBr) 1680 (C=O); EI MS (rel int) 349/351 (parent, Br^{79}/Br^{81}, 25/33), 270 (80), 242 (95), 216 (100), 91 (80); HRMS calcd for $C_{16}H_{13}NOBrCl$ 348.9869, found 348.988 27.

***N-tert*-Butyl-2-(3-bromo-2-oxo-5-phenyl-8-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (40c)** was prepared according to method A: mp 211–213 °C; 66% yield, as a mixture of diastereomers; ^{1}H-NMR (δ, $CDCl_3$) 1.33 (s, 9H), 2.8–3.0 (m, 2H), 4.24 (m, 1H), 4.5 (m's, 2H), 4.75

(m, 1H), 6.04 (bs, 1H), 6.61 (d, J = 8, 1H), 7.01 (d, J = 2, 1H), 7.1–7.4 (m, 6H); ^{13}C-NMR (δ, $CDCl_3$) 28.7, 43.5, 45.3, 46.8, 51.7, 54.3, 56.3, 123.5, 127.4, 127.5, 128.6, 128.8, 129.1, 133.3, 136.6, 138.8, 142.0, 166.5, 167.8; IR (cm^{-1}, KBr) 1660, 1670 (C=O); EI MS (rel int) 463/465 (parent + 1, Br^{79}/Br^{81}, 64/78), 392 (100), 282 (54); HRMS calcd for $C_{22}H_{24}N_2O_2BrCl$ 462.0709, found 462.073 88.

***N-tert*-Butyl 2-(3-azido-2-oxo-5-phenyl-8-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (41c)** was prepared according to method A: mp 124–127 °C; 73% yield of a mixture of diastereomers; ^{1}H-NMR (δ, $CDCl_3$) 1.29 and 1.34 (s's, 9H), 2.4–3.0 (m, 2H), 3.06 and 4.37 (AB q's, J_{AB} = 15 and 15, $\Delta\nu$ = 249 and 46, 2H), 3.81 and 3.91 (m's, 1H), 4.20 and 4.70 (m's, 1H), 5.90 and 6.00 (bs's, 1H), 6.61 and 7.0 (d, J = 8 and m, 1H), 7.1–7.4 (m, 6H); ^{13}C-NMR (δ, $CDCl_3$) 28.6, 28.7, 39.5, 41.6, 43.2, 51.7, 53.4, 54.2, 58.8, 123.4, 126.0, 126.1, 126.7, 126.8, 127.3, 127.6, 127.7, 128.6, 128.8, 131.2, 133.3, 136.5, 137.0, 139.0, 141.3, 142.2, 166.5, 170.2; IR (cm^{-1}, KBr) 2100 (N_3), 1670 (C=O); FAB MS (rel int) 426 (parent + 1, 100), 353 (88), 228 (37); HRMS calcd for $C_{22}H_{24}N_5O_2Cl$ 425.1685, found 425.178 49.

***N-tert*-Butyl 2-(3-amino-2-oxo-5-phenyl-8-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (42c)** was prepared according to method D: mp 68–78 °C; 100% yield, as a mixture of isomers; ^{1}H-NMR (δ, $CDCl_3$) 1.26 and 1.31 (s's, 9H), 2.03 and 2.5–2.8 (m, 3H), 3.44 and 4.32 (m and s, 2H), 4.13 and 4.30 (m's, 1H), 5.81 and 6.03 (bs's, 1H), 6.56 and 6.9–7.5 (d, J = 8 and m, 9H); ^{13}C-NMR (δ, $CDCl_3$) 28.6, 28.7, 39.6, 39.7, 42.2, 44.0, 50.6, 50.7, 51.4, 51.7, 53.5, 53.8, 123.1, 125.8, 126.2, 126.4, 126.9, 127.3, 128.3, 128.7, 128.8, 128.9, 131.1, 132.8, 134.0, 137.4, 139.7, 141.8, 142.8, 166.9, 167.6, 175.1, 175.9; IR (cm^{-1}, KBr) 1660, 1680 (C=O); FAB MS (rel int) 401 (parent + 1, 100), 327 (97), 272 (43), 228 (42). Anal. ($C_{22}H_{26}N_3O_2Cl\cdot{}^2/_3H_2O$) C, H, N.

***N-tert*-Butyl 2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-8-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]-ethanoic acid amide (43c)** was prepared according to method A in 37% yield for the *cis* stereoisomer after column chromatography: mp 239–243 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.29 (s, 9H), 2.8–3.1 (m, 2H), 3.27 (AB q, J_{AB} = 16, $\Delta\nu$ = 267, 2H), 4.26 (d, J = 8, 1H), 4.55 (dd, J = 9, 11, 1H), 5.67 (bs, 1H), 6.8–7.6 (m, 14H); ^{13}C-NMR (δ, $CDCl_3$) 28.7, 36.9, 43.9, 50.3, 52.0, 53.0, 117.1, 119.3, 122.6, 125.0, 126.2, 126.8, 127.9, 128.4, 129.7, 131.8, 134.5, 136.8, 140.3, 141.2, 142.0, 154.8, 166.7, 172.9; IR (cm^{-1}, KBr) 1640, 1650, 1680 (C=O); EI MS (rel int) 552 (parent, 5), 356 (45), 255 (55), 153 (100), 127 (55), 57 (40); HRMS calcd for $C_{29}H_{30}Cl_2N_4O_3$ 554.1668, found 554.166 96. Anal. ($C_{29}H_{30}Cl_2N_4O_3\cdot{}^1/_4H_2O$) C, H, N.

Preparation of *tert*-Butyl 2-[3-(3-(3-Chlorophenyl)-ureido)-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoate (43d). *tert*-Butyl 2-(3-bromo-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoate (40d) was prepared according to method A, using *tert*-butyl iodoacetate as the alkylating agent: mp 135–138 °C; 97% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.46 (s, 9H), 2.29 (s, 3H), 2.83 (m, 1H), 2.96 (m, 1H), 4.50 (AB q, J_{AB} = 17, $\Delta\nu$ = 128, 2H), 4.58 (dd, J = 8, 12, 1H), 4.99 (m, 1H), 6.59 (d, J = 7, 1H), 6.88 (d, J = 8, 1H), 6.95 (s, 1H), 7.2–7.4 (m, 4H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 28.1, 43.3, 45.7, 47.4, 52.0, 82.1, 123.1, 127.2, 127.8, 128.0, 128.6, 128.9, 135.2, 137.7, 139.7, 140.5, 167.49, 167.53; IR (cm^{-1}, KBr) 1692, 1743 (C=O); FAB MS (rel int) 444/446 (parent + 1, Br^{79}/Br^{81}, 9/9), 388/390 (Br^{79}/Br^{81}, 100/98), 310 (82); HRMS calcd for $C_{23}H_{26}NO_3Br$ 443.1096, found 443.103 74. Anal. ($C_{23}H_{26}NO_3Br$) H, N; C: calcd 62.17, found 62.66.

***tert*-Butyl 2-(3-azido-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoate (41d)** was prepared according to method A as a foam (mixture of diastereomers) which was used directly in the next step: ^{1}H-NMR (δ, $CDCl_3$) 1.44 (s, 9H), 2.30 and 2.33 (s's, 3H), 2.7–3.0 (m, 2H), 3.6–5.0 (series of multiplets, 4H), 6.8–7.4 (m, 8H); IR (cm^{-1}, KBr) 2107 (N_3), 1679, 1742 (C=O); FAB MS (rel int) 407 (parent + 1, 23), 351 (94), 204 (100); HRMS calcd for $C_{23}H_{26}N_4O_3$ 406.1999, found 406.196 88.

***tert*-Butyl 2-(3-amino-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoate (42d)** was prepared according to method A as a foam in 85% overall yield for two steps, as a mixture of diastereomers (data reported for major, *cis*, isomer): ^{1}H-NMR (δ, $CDCl_3$) 1.41 (s, 9H), 2.30 (s, 3H), 2.53 (m, 1H), 2.77 (m, 1H), 3.21 (AB q, J_{AB} = 17, $\Delta\nu$ = 258, 2H), 3.51 (m, 1H), 4.13 (m, 1H), 6.8–7.4 (m, 10H); ^{13}C-NMR (δ, $CDCl_3$) 28.0, 40.1, 44.2, 50.5, 50.6, 51.5, 53.4, 81.7, 124.9, 126.1, 126.3, 127.6, 128.2, 128.5, 129.0, 130.0, 136.0, 138.5, 141.4, 168.8, 174.8; IR (cm^{-1}, KBr) 1670, 1742 (C=O); FAB MS (rel int) 381 (parent + 1, 26), 325 (100), 254 (46); HRMS calcd for $C_{23}H_{28}N_2O_3$ 380.2099, found 380.209 31.

***tert*-Butyl 2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoate (43d)** was prepared according to method A, and the diastereomers were separated by crystallization from methylene chloride:ethyl acetate to give mp 230–235 °C, 62% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.37 (s, 9H), 2.29 (s, 3H), 2.61 (m, 1H), 3.00 (m, 1H), 3.21 (AB q, J_{AB} = 17, $\Delta\nu$ = 189, 2H), 4.15 (m, 1H), 4.57 (m, 1H), 6.8–7.4 (m, 14H); ^{13}C-NMR (δ, $CDCl_3$) 21.1, 27.9, 38.0, 43.8, 49.4, 51.7, 82.3, 116.9, 118.8, 122.0, 125.1, 126.2, 126.3, 128.3, 128.5, 129.4, 130.5, 134.1, 135.5, 139.0, 140.6, 140.7, 142.3, 154.6, 168.1, 172.8; IR (cm^{-1}, KBr) 1646, 1694, 1745 (C=O); FAB MS (rel int) 534/536 (parent + 1, Cl^{35}/Cl^{37}, 10/3), 351 (43), 325 (100), 254 (42). Anal. ($C_{30}H_{32}N_3O_4Cl\cdot{}^1/_4H_2O$) C, H, N.

Single-Crystal X-ray Analysis of 43d. A representative crystal was surveyed, and a 1 Å data set (maximum sin λ/ν = 0.5) was collected on a Siemens R3RA/v diffractometer. Atomic scattering factors were taken from ref 36. All crystallographic calculations were facilitated by the SHELXTL[37] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table E1 (supplementary material). A trial structure was obtained by direct methods. This trial structure was refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogen on nitrogen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R index was 6.19%. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package. Coordinates, anisotropic temperature factors, distances and angles are available as supplementary material (Tables E2–E6).

Preparation of *N-tert*-Butyl 2-[3-(3-(3-Chlorophenyl)-ureido)-2-oxo-5-cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (*Cis* and *Trans* Isomers 58c and 58t). 2-Cyclohexyl-2-phenylethanol (46). To a 500 mL round-bottomed flask equipped with condenser and N_2 inlet were added 15 g (68.8 mmol) of α-phenylcyclohexylacetic acid, 110 mL of dry tetrahydrofuran, and 137 mL (275 mmol) of a 2 M solution of borane–methyl sulfide in tetrahydrofuran. The solution was refluxed 60 h, cooled, and evaporated. The residue was taken up carefully in 200 mL of ethanol, treated with 2 g of sodium carbonate, and refluxed for 3 h. The reaction mixture was cooled, evaporated, taken up in ethyl acetate:water, and separated, and the aqueous phase was extracted with fresh ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, and evaporated to an oil which solidified on standing. The yield was 12.27 g (87%): ^{1}H-NMR (δ, $CDCl_3$) 0.7–1.9 (m, 11H), 2.54 (m, 1H), 3.7–3.9 (m, 2H), 7.1–7.3 (m, 5H).

2-Cyclohexyl-2-phenylethanol Tosylate (47). To a 125 mL round-bottomed flask were added 12.27 g (60.15 mmol) of **46** and 30 mL of dry pyridine. The reaction mixture was cooled to 0 °C, and 13.78 g (72.18 mmol) of tosyl chloride was added. The reaction mixture was let stand at 0 °C for 14 h, poured into water, and extracted into ether. The ether layer was washed with 3 portions of 1 N hydrochloric acid, 3 portions of saturated aqueous sodium bicarbonate solution, 2 portions of water, and brine, dried over sodium sulfate, and evaporated. The residue was slurried in ethanol and collected by filtration to afford a white solid: mp 95–100 °C; 13.1 g (61%); ^{1}H-NMR (δ, $CDCl_3$) 0.6–1.7 (m, 11H), 2.40 (s, 3H), 2.64 (m, 1H), 4.1–

4.3 (m, 2H), 6.9–7.5 (m, 5H); IR (cm^{-1}, KBr) 2940 (C-H) and 1600 (C=C); MS (rel int) 186 (100, parent for elimination of tosic acid), 104 (95), 91 (70). Anal. ($C_{21}H_{26}O_3S$) C, H.

2-Cyclohexyl-2-phenyl-1-iodoethane (48). To a 250 mL round-bottomed flask equipped with condenser and N_2 inlet were added 13.9 g (39.4 mmol) of **47**, 80 mL of acetone, and 6.49 g (43.3 mmol) of sodium iodide. The reaction was refluxed 36 h, cooled, and evaporated. The residue was taken up in ethyl acetate, washed with water and aqueous sodium bisulfite solution, dried over sodium sulfate, and evaporated to an oil, 12.11 g (98%), which was used directly in the next step: ^{1}H-NMR (δ, $CDCl_3$) 0.7–1.9 (m, 11H), 2.60 (m, 1H), 3.4 and 3.6 (m, 2H), 7.0–7.3 (m, 5H).

Diethyl (2-Cyclohexyl-2-phenylethyl)malonate (49). To a 500 mL round-bottomed flask equipped with condenser and N_2 inlet were added 3.05 g (77.1 mmol) of sodium hydride, which was washed with hexane and the hexane pipetted off, and 100 mL of dry tetrahydrofuran. To the stirring suspension was added a solution of 12.34 g (77.1 mmol) of diethyl malonate in 50 mL of dry tetrahydrofuran dropwise over 30 min. Once gas evolution had ceased, a solution of 12.11 g (38.57 mmol) of **48** in 40 mL of dry tetrahydrofuran was added, and the reaction mixture was refluxed 3 days. The reaction mixture was concentrated, poured into 1 N hydrochloric acid, and extracted twice into ethyl acetate. The combined organic layer was washed with water, 3 portions of aqueous sodium bisulfite solution, and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane: ethyl acetate as eluant to afford an oil, 12.53 g (87%): ^{1}H-NMR (δ, $CDCl_3$) 0.6–2.0 (m, 12H), 1.12 (t, J = 7, 3H), 1.20 (t, J = 7, 3H), 2.24 (m, 1H), 2.32 (m, 1H), 2.95 (dd, J = 4, 10, 1H), 3.98 (m, 2H), 4.15 (m, 2H), 6.9–7.2 (m, 5H); ^{13}C-NMR (δ, $CDCl_3$) 13.9, 14.1, 26.4, 26.5, 31.1, 31.2, 32.0, 43.3, 49.7, 50.3, 61.0, 61.2, 126.3, 128.2, 128.5, 142.6, 169.4, 169.6; IR (cm^{-1}, KBr) 1738 (C=O); MS (rel int) 346 (parent, 12), 160 (100), 114 (60), 28 (59); HRMS calcd for $C_{21}H_{30}O_4$ 346.2136, found 346.218 38.

3-Cyclohexyl-3-phenylbutanoic Acid (50). To a 250 mL round-bottomed flask equipped with condenser and N_2 inlet were added 12.53 g (36.2 mmol) of **49**, 80 mL of acetic acid, and 25 mL of 6 N hydrochloric acid. The reaction mixture was refluxed 20 h, cooled, poured into water, and extracted into ethyl acetate. The organic phase was washed with water and brine, dried over sodium sulfate, and evaporated. Evaporation from heptane removed traces of water to afford an oil, 9.78 g (99% crude yield): ^{1}H-NMR (δ, $CDCl_3$) 0.8–2.3 (m, 16H), 7.0–7.3 (m, 5H); ^{13}C-NMR (δ, $CDCl_3$) 26.5, 27.7, 31.2, 31.3, 32.6, 43.2, 51.6, 126.2, 128.3, 128.5, 143.3, 180.8; IR (cm^{-1}, KBr) 1720 (C=O); MS (rel int) 246 (parent, 13), 173 (45), 163 (52), 117 (78), 104 (100), 91 (79), 55 (48); HRMS calcd for $C_{16}H_{22}O_2$ 246.1614, found 246.159 68.

4-Cyclohexyl-1,2,3,4-tetrahydronaphth-1-one (51) was prepared according to method F as an oil in 74% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.9–2.1 (m, 5H), 1.4–1.8 (m, 6H), 2.0–2.2 (m, 2H), 2.4–2.7 (m, 3H), 7.0–7.3 (m, 3H), 7.88 (m, 1H); ^{13}C-NMR (δ, $CDCl_3$) 24.3, 26.3, 26.5, 30.5, 35.0, 39.9, 44.0, 126.6, 127.4, 129.2, 132.3, 132.6, 147.3, 198.6; IR (cm^{-1}, KBr) 1690 (C=O); MS (rel int) 228 (parent, 7), 146 (100), 55 (20); HRMS calcd for $C_{16}H_{20}O$ 228.1509, found 228.150 16.

4-Cyclohexyl-1,2,3,4-tetrahydronaphth-1-one oxime (52) was prepared according to method C: mp 120–123 °C; 71% yield; ^{1}H-NMR (δ, $CDCl_3$) 0.8–1.7 (m, 11H), 1.88 (m, 1H), 2.12 (m, 1H), 2.39 (m, 1H), 2.79 (m, 2H), 7.0–7.3 (m, 3H), 7.77 (m, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.5, 22.4, 26.3, 26.4, 31.0, 32.0, 38.8, 44.9, 124.6, 126.6, 128.5, 129.7, 129.9, 143.2, 155.6; IR (cm^{-1}, KBr) 1640 (weak) (C=N). Anal. ($C_{16}H_{21}NO$) C, H, N.

5-Cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (53) was prepared according to method G: mp 125–128 °C; 80% yield; ^{1}H-NMR (δ, $CDCl_3$) 0.6–2.0 (m, 12H), 2.2–2.4 (m, 3H), 2.59 (m, 1H), 6.9–7.2 (m, 4H), 8.80 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 26.3, 26.4, 31.0, 31.6, 32.5, 32.7, 38.7, 45.8, 122.4, 125.3, 126.9, 128.6, 136.3, 138.2, 176.1; IR (cm^{-1}, KBr) 1680 (C=O); MS (rel int) 243 (40, parent), 160 (100), 132 (32), 118 (37). Anal. ($C_{16}H_{21}NO$) C, H, N.

3-Bromo-5-cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (54) was prepared according to method A: mp 104–107 °C; 54% yield; ^{1}H-NMR (δ, $CDCl_3$) 0.6–2.0 (m, 11H), 2.25 (m, 1H), 2.69 (m, 2H), 4.37 (dd, J = 7, 11, 1H), 7.0–7.3 (m, 4H), 8.90 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 26.1, 26.4, 30.3, 32.3, 38.0, 44.2, 44.9, 48.0, 123.1, 126.5, 126.9, 127.2, 135.3, 137.3, 169.6.

***N-tert*-Butyl-2-(3-bromo-2-oxo-5-cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (*cis* and *trans* isomers 55c and 55t)** were prepared according to method A, as a mixture of diastereomers, which separated into the less polar isomer, mp 188–189.5 °C, 36% yield, and the more polar isomer, mp 190.5–192 °C, 58% yield.

Less polar, *cis* isomer 55c: ^{1}H-NMR (δ, $CDCl_3$) 0.4–2.0 (m, 11H), 1.36 (s, 9H), 2.39 (m, 1H), 2.61 (m, 2H), 4.01 (AB q, J_{AB} = 15, Δν = 381, 2H), 4.59 (dd, J = 8, 12, 1H), 6.25 (bs, 1H), 6.9–7.4 (m, 4H); ^{13}C-NMR (δ, $CDCl_3$) 26.1, 26.2, 28.7, 32.2, 32.5, 40.1, 42.5, 47.4, 50.3, 51.5, 55.7, 124.7, 127.5, 128.6, 131.4, 136.0, 141.4, 167.6, 168.6.

More polar, *trans* isomer 55t: ^{1}H-NMR (δ, $CDCl_3$) 0.6–1.9 (m, 11H), 1.31 (s, 9H), 2.06 (m, 1H), 2.65 (m, 2H), 4.26 (AB q, J_{AB} = 15, Δν = 32, 2H), 4.2 (m, 1H), 6.22 (bs, 1H), 7.1–7.3 (m, 4H); ^{13}C-NMR (δ, $CDCl_3$) 26.0, 26.3, 26.4, 28.7, 30.3, 32.0, 37.7, 43.7, 45.4, 48.1, 51.4, 54.8, 123.6, 126.1, 127.5, 127.6, 127.7, 136.2, 142.0, 167.1, 168.4.

***N-tert*-Butyl-2-(3-azido-2-oxo-5-cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (*cis* isomer 56c)** was prepared according to method A, from the more polar, *trans* diastereomer in the previous step in 47% yield, mp 136–139 °C: ^{1}H-NMR (δ, $CDCl_3$) 0.4–2.0 (m, 11H), 1.34 (s, 9H), 2.22 (m, 1H), 2.43 (m, 2H), 3.84 (m, 1H), 4.04 (AB q, J_{AB} = 15, Δν = 291, 2H), 6.32 (bs, 1H), 7.0–7.4 (m, 4H); ^{13}C-NMR (δ, $CDCl_3$) 26.0, 26.1, 26.2, 28.6, 32.2, 32.5, 36.6, 40.2, 47.7, 51.5, 55.1, 58.4, 124.6, 127.4, 128.6, 131.3, 136.4, 140.7, 167.7, 170.8; IR (cm^{-1}, KBr) 2090 (N_3), 1650, 1675 (C=O); FAB MS (rel int) 398 (parent + 1, 100), 372 (67), 325 (86), 130 (40).

***N-tert*-Butyl-2-(3-azido-2-oxo-5-cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (*trans* isomer 56t)** was prepared according to method A, from the more polar, *cis* diastereomer in the previous step in 70% yield, mp 160–163 °C: ^{1}H-NMR (δ, $CDCl_3$) 0.7–2.0 (m, 12H), 1.31 (s, 9H), 2.30 (m, 1H), 2.68 (m, 1H), 3.60 (dd, J = 8, 13, 1H), 4.26 (AB q, J_{AB} = 15, Δν = 79, 2H), 6.25 (bs, 1H), 7.1–7.3 (m, 4H); ^{13}C-NMR (δ, $CDCl_3$) 26.0, 26.3, 28.7, 30.3, 32.0, 37.8, 39.3, 41.6, 51.4, 54.0, 59.5, 123.6, 126.0, 127.4, 127.7, 136.6, 141.4, 167.2, 170.6; IR (cm^{-1}, KBr) 2090 (N_3), 1650, 1680 (C=O); FAB MS (rel int) 398 (parent + 1, 78), 372 (100), 325 (68), 130 (57), 118 (55). Anal. ($C_{22}H_{31}N_5O_2$) C, H, N.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (*cis* isomer 57c)** was prepared according to method A, mp 105–115 °C, in quantitative yield: ^{1}H-NMR (δ, $CDCl_3$) 0.4–1.7 (m, 10H), 1.31 (s, 9H), 1.98 (m, 1H), 2.18 (m, 1H), 2.39 (m, 1H), 2.62 (m, 1H), 3.79 (m, 1H), 4.08 (AB q, J_{AB} = 15, Δν = 364, 2H), 5.5 (bs, 2H), 6.61 (bs, 1H), 7.0–7.3 (m, 4H); ^{13}C-NMR (δ, $CDCl_3$) 25.9, 26.2, 28.7, 32.2, 32.3, 37.7, 39.9, 47.9, 50.6, 51.7, 54.1, 124.1, 127.3, 128.5, 131.6, 136.6, 140.4, 167.7, 172.1; IR (cm^{-1}, KBr) 1670 (C=O); FAB MS (rel int) 372 (parent + 1, 96), 299 (100), 243 (37); HRMS calcd for $C_{22}H_{34}N_3O_2$ 372.2651, found 372.265 48.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (*trans* isomer 57t)** was prepared according to method A, mp 292–294 °C, in quantitative yield: ^{1}H-NMR (δ, $CDCl_3$) 0.7–1.7 (m, 10H), 1.25 (s, 9H), 2.00 (m, 1H), 2.20 (m, 1H), 2.81 (m, 1H), 3.64 (m, 1H), 4.33 (AB q, J_{AB} = 15, Δν = 96, 2H), 7.04 (bs, 2H), 7.23 (m, 4H); ^{13}C-NMR (δ, $CDCl_3$) 26.0, 26.2, 28.5, 30.1, 31.8, 49.8, 50.1, 51.1, 51.6, 52.6, 123.4, 126.4, 127.7, 136.2, 140.4, 167.3; IR (cm^{-1}, KBr) 1655, 1675 (C=O); FAB MS (rel int) 372 (parent + 1, 100), 299 (70), 243 (27); HRMS calcd for $C_{22}H_{34}N_3O_2$ 372.2651, found 372.2641.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]-ethanoic acid amide (58c)** was prepared according to method A: mp 223–226 °C; 48% yield; ^{1}H-NMR (δ, $CDCl_3$) 0.52 (m, 1H), 0.8–1.8 (m, 9H), 1.37 (s, 9H), 1.98 (m, 1H), 2.13 (m, 1H), 2.48 (m, 1H), 2.58 (m, 1H), 4.23 (AB q, J_{AB} = 16, Δν

= 408, 2H), 4.48 (m, 1H), 6.28 (s, 1H), 6.39 (d, J = 7, 1H), 6.8–7.3 (m, 7H), 7.55 (s, 1H), 8.01 (s, 1H); ^{13}C-NMR (δ, $CDCl_3$) 26.1, 26.2, 28.7, 32.3, 32.5, 37.2, 40.3, 48.2, 50.7, 52.1, 53.6, 116.9, 118.9, 119.0, 122.1, 123.0, 127.4, 128.6, 129.4, 131.8, 134.2, 136.6, 140.5, 140.7, 155.2, 167.4, 174.5; IR (cm^{-1}, KBr) 1640, 1650, 1680 (C=O); FAB MS (rel int) 525 (parent + 1, 45), 452 (37), 357 (50), 284 (75), 119 (100). Anal. ($C_{29}H_{37}ClN_4O_3 \cdot {}^1/_4H_2O$) C, H, N.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-cyclohexyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]-ethanoic acid amide (58t, *trans* isomer)** was prepared according to method A: mp 292–297 °C (from 1,2-dichloroethane:isopropyl ether); 17.5% yield; ^{1}H-NMR (δ, $CDCl_3$) 0.69 (m, 1H), 0.92 (m, 1H), 1.0–1.9 (m, 8H), 1.34 (s, 9H), 2.08 (m, 2H), 2.52 (m, 1H), 4.26 (dd, J = 8, 11, 1H), 4.45 (AB q, J_{AB} = 16, $\Delta\nu$ = 62, 2H), 7.0–7.4 (m, 9H); ^{13}C-NMR (δ, $CDCl_3$) 25.9, 26.2, 28.2, 30.2, 31.9, 37.5, 40.3, 47.8, 51.6, 53.2, 53.5, 121.0, 123.1, 123.2, 126.4, 126.7, 128.1, 128.8, 130.7, 135.4, 136.5, 136.9, 139.8, 156.9, 168.7, 174.4; IR (cm^{-1}, KBr) 1640, 1650, 1680 (C=O); FAB MS (rel int) 525 (parent + 1, 20), 372 (58), 309 (100); HRMS calcd for $C_{29}H_{37}ClN_4O_3$ 524.2554, found 524.256 94. Anal. ($C_{29}H_{37}ClN_4O_3 \cdot {}^1/_3(C_2H_6Cl_2)$) C, H, N.

Preparation of *N-tert*-Butyl 2-[3-(3-(3-Chlorophenyl)-ureido)-2-oxo-5-cyclohexyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (68a). Method I. Preparation of 3-Cyclohexyl-3-(4-tolyl)butanoic Acid (60a). 5-(4-Tolyl)-5-cyclohexylbutyrolactone (59a). To a 500 mL round-bottomed flask equipped with a N_2 inlet were added 26.67 g (121 mmol) of ethyl 2-(4-toluyl)propionate[38] and 275 mL of dry tetrahydrofuran. The solution was cooled to 3 °C, and a 2 N solution of cyclohexylmagnesium chloride, 66 mL (133 mmol), was added dropwise over 20 min. The reaction mixture was then warmed to room temperature and stirred for 3 h. The reaction mixture was poured into saturated aqueous ammonium chloride solution and extracted into ethyl acetate. The organic layer was washed with more ammonium chloride and brine, dried over sodium sulfate, and evaporated. The product gave R_f = 0.25 compared to starting material at R_f = 0.30 in 8:1 hexane:ethyl acetate on silica gel and was used directly in the following step.

3-Cyclohexyl-3-(4-tolyl)butanoic Acid (60a). The resulting orange oil was dissolved in 121 mL of trifluoroacetic acid, heated to reflux, and treated with 58 mL (0.364 mol) of triethylsilane dropwise over 5 h. Refluxing was continued for 3 days, and the reaction mixture was poured into water and extracted into ethyl acetate. The organic layer was washed with water, aqueous sodium bicarbonate solution, and brine, dried over magnesium sulfate, filtered, and evaporated. The residue was taken up in aqueous sodium hydroxide solution, washed with ethyl acetate, acidified with hydrochloric acid, extracted into ethyl acetate, dried, and evaporated. The resulting oil gave 17.94 g (57%): ^{1}H-NMR (δ, $CDCl_3$) 0.6–2.4 (m, 16H), 2.28 (s, 3H), 6.9–7.2 (m, 4H); MS (rel int) 260 (parent, 22), 177 (80), 131 (100), 55 (45), 41 (50).

4-Cyclohexyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one (61a) was prepared according to method F as an oil in 18% yield: ^{1}H-NMR (δ, $CDCl_3$) 0.9–1.4 (m, 6H), 1.5–1.9 (m, 6H), 2.0–2.2 (m, 2H), 2.33 (s, 3H), 2.5–2.8 (m, 2H), 7.1 (m, 1H), 7.25 (m, 1H), 7.80 (s, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.9, 24.4, 26.4, 26.5, 30.5, 31.9, 35.1, 40.0, 43.7, 127.5, 127.6, 129.1, 132.2, 133.5, 136.2, 144.4, 198.9; IR (cm^{-1}, KBr) 1682 (C=O); MS (rel int) 242 (parent, 20), 160 (100); HRMS calcd for $C_{17}H_{22}O$ 242.1665, found 242.165 62.

4-Cyclohexyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one oxime (62a) was prepared according to method C as an oil, which was used directly in the next step: ^{1}H-NMR (δ, $CDCl_3$) 0.9–2.4 (m, 14H), 2.325 (s, 3H), 2.80 (m, 2H), 6.98 (m, 1H), 7.07 (m, 1H), 7.64 (s, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.4, 21.1, 22.5, 26.4, 31.0, 32.0, 38.9, 44.5, 124.9, 129.4, 129.5, 129.7, 136.0, 140.3, 155.9; MS (rel int) 257 (parent, 15), 174 (100); HRMS calcd for $C_{17}H_{23}NO$ 257.1776, found 257.179 03.

5-Cyclohexyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (63a) was prepared according to method G: mp 171–173 °C; 79% yield; ^{1}H-NMR (δ, $CDCl_3$) 0.6–2.0 (multiplets, 13H), 2.1–2.4 (m, 2H), 2.28 (s, 3H), 2.53 (m, 1H), 6.82 (s, 1H), 6.91 (m, 1H), 7.05 (m, 1H), 8.83 (s, 1H, N*H*); ^{13}C-NMR (δ, $CDCl_3$) 20.8, 26.3, 26.4, 26.5, 31.0, 31.7, 32.5, 32.7, 38.8, 45.5, 123.0, 126.0, 128.4, 133.1, 136.7, 138.0, 176.3; IR (cm^{-1}, KBr) 1670 (C=O); MS (rel int) 257 (parent, 30), 174 (100). Anal. ($C_{17}H_{23}NO$) C, H, N.

3-Bromo-5-cyclohexyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (64a) was prepared according to method A as a foam in 100% yield, which was triturated with methylene chloride and hexane to give a solid, mp 124–148 °C, mixture of diastereomers: ^{1}H-NMR (δ, $CDCl_3$) 0.4–2.0 (m, 12H), 2.29 (s, 3H), 2.4–2.9 (m, 2H), 4.37 and 4.62 (multiplets, 1H, diastereomers), 6.9–7.1 (m, 3H), 8.67 and 8.82 (singlets, 1H, diastereomers); ^{13}C-NMR (δ, $CDCl_3$) 20.8, 26.1, 26.2, 26.3, 26.4, 30.3, 32.0, 32.1, 32.3, 38.0, 39.7, 42.7, 43.9, 45.0, 47.3, 48.2, 48.8, 123.6, 123.8, 126.7, 126.9, 127.2, 131.4, 132.2, 132.3, 135.9, 137.1, 137.2, 137.9, 169.7, 170.1; IR (cm^{-1}, KBr) 1670 (C=O); MS (rel int) 336/338 (100/95, parent for Br^{79}/Br^{81}), 258 (75); HRMS calcd for $C_{17}H_{22}BrNO$ 335.0885, found 335.090 19. Anal. ($C_{17}H_{22}BrNO$) C, H, N.

***N-tert*-Butyl-2-(3-bromo-2-oxo-5-cyclohexyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (65a)** was prepared according to method A as a mixture of isomers which was chromatographed on silica gel with hexane:ethyl acetate to afford the two diastereomeric products, the less polar, *cis* isomer, mp 183–186 °C, 2.16 g, 34% yield, and the more polar, *trans* isomer, mp 206.5–207.5 °C, 3.16 g, 50% yield.

Less polar isomer (*cis*): ^{1}H-NMR (δ, $CDCl_3$) 0.4–2.0 (m, 14H), 1.36 (s, 9H), 2.305 (s, 3H), 2.36 (m, 1H), 2.59 (m, 2H), 4.05 (AB q, J_{AB} = 14, $\Delta\nu$ = 372, 2H), 4.59 (dd, J = 8, 12, 1H), 6.24 (bs, 1H), 6.8–7.2 (m, 3H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 26.0, 26.1, 26.25, 28.7, 32.2, 32.5, 40.2, 42.5, 47.5, 49.8, 51.5, 55.8, 125.2, 128.2, 131.2, 132.9, 138.7, 141.2, 167.6, 168.7; IR (KBr, cm^{-1}) 1682, 1658 (C=O); MS (rel int) 449/451 (70/65, parent for Br^{79}/Br^{81}), 376/378 (100/95); HRMS calcd for $C_{23}H_{33}BrN_2O_2$ 448.1725, found 448.174 05. Anal. ($C_{23}H_{33}BrN_2O_2$) C, H, N.

More polar isomer (*trans*): ^{1}H-NMR (δ, $CDCl_3$) 0.6–1.9 (m, 11H), 1.33 (s, 9H), 2.05 (m, 1H), 2.31 (s, 3H), 2.62 (m, 2H), 4.26 (AB q, J_{AB} = 14, $\Delta\nu$ = 23, 2H), 4.2 (m, 1H), 6.24 (bs, 1H), 7.0–7.2 (m, 3H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 26.0, 26.3, 26.4, 28.7, 30.3, 32.0, 37.7, 43.5, 45.5, 48.2, 51.4, 54.9, 124.2, 125.9, 128.4, 133.1, 137.7, 141.8, 167.2, 168.7; IR (KBr, cm^{-1}) 1660 (C=O); MS (rel int) 449/451 (72/68, parent for Br^{79}/Br^{81}), 376/378 (100/95). Anal. ($C_{23}H_{33}BrN_2O_2$) C, H, N.

***N-tert*-Butyl-2-(3-azido-2-oxo-5-cyclohexyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (66a)** was prepared from the more polar, *trans* isomer of **65a** according to method A as a white solid: mp 166–169 °C; 2.065 g (72.5%), *cis* diastereomer; ^{1}H-NMR (δ, $CDCl_3$) 0.4–2.0 (m, 12H), 1.36 (s, 9H), 2.22 (m, 1H), 2.30 (s, 3H), 2.40 (m, 2H), 3.88 (dd, J = 6, 12, 1H), 4.05 (AB q, J_{AB} = 14, $\Delta\nu$ = 384, 2H), 6.31 (bs, 1H), 6.8–6.9 (m, 2H), 7.24 (s, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 26.0, 26.1, 26.2, 28.7, 32.2, 32.5, 36.6, 40.3, 47.2, 51.5, 55.1, 58.5, 125.1, 128.1, 131.1, 133.2, 138.7, 140.5, 167.7, 171.0; IR (KBr, cm^{-1}) 2110 (N_3), 1678, 1658 (C=O); FAB MS (rel int) 412 (parent + 1, 83), 386 (67), 339 (100), 144 (76). Anal. ($C_{23}H_{33}N_5O_2$) C, H, N.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-cyclohexyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (67a)** was prepared according to method A: mp 177–180 °C, 1.86 g (96%); ^{1}H-NMR (δ, $CDCl_3$) 0.4–2.0 (m, 13H), 1.36 (s, 9H), 2.28 (s, 3H), 2.3–2.5 (m, 2H), 3.47 (dd, J = 7, 12, 1H), 4.03 (AB q, J_{AB} = 15, $\Delta\nu$ = 378, 2H), 6.23 (bs, 1H), 6.87 (m, 2H), 7.24 (s, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 26.1, 26.2, 26.3, 28.7, 32.3, 32.6, 40.3, 41.1, 47.9, 50.9, 51.4, 54.9, 124.8, 127.6, 131.0, 134.2, 138.1, 141.0, 168.1, 176.2; IR (KBr, cm^{-1}) 1666 (C=O); FAB MS (rel int) 387 (parent + 2, 100), 313 (97); HRMS calcd for $C_{23}H_{35}N_3O_2$ 385.2721, found 385.271 57.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-cyclohexyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (68a)** was prepared according to method A: mp 181–184 °C from methylene chloride:cyclohexane; 52% yield; ^{1}H-NMR (δ, $CDCl_3$) 0.4–1.8 (m's, 10H), 1.40 (s, 9H), 1.94 (m, 1H), 2.06 (t, J = 13, 1H), 2.31 (s, 3H), 2.46 (q, J = 10, 1H), 2.55 (m, 1H), 4.23 (AB q, J = 16, $\Delta\nu$ = 419, 2H), 4.48 (m, 1H), 6.28 (bs, 1H), 6.38 (d, J = 6, 1H), 6.7–7.0 (m, 6H), 7.55 (bs, 1H), 7.93 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 26.1,

26.3, 28.7, 32.3, 32.6, 37.1, 40.4, 47.8, 50.8, 52.1, 53.5, 116.9, 119.0, 122.2, 123.7, 128.1, 129.4, 131.6, 133.4, 134.2, 138.5, 140.4, 155.2, 167.4, 174.9; IR (cm^{-1}, KBr) 1650, 1680 (C=O); FAB MS (rel int) 539 (parent, 17), 414 (75), 158 (65), 144 (93), 132 (100). Anal. ($C_{30}H_{39}ClN_4O_3$) C, H, N.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-benzyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (68b).**

4-Benzyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one oxime (62b) was prepared from 4-benzyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one, **61b**, according to method C in 60% yield as a light yellow solid: ^{1}H-NMR (δ, $CDCl_3$) 1.82 (m, 2H), 2.35 (s, 3H), 2.7–3.1 (m, 5H), 6.9–7.4 (m, 7H), 7.74 (bs, 1H), 9.2 (m, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.0, 21.2, 24.0, 40.2, 41.0, 124.5, 124.6, 126.1, 128.3, 128.4, 129.1, 129.6, 130.2, 136.2, 140.1, 140.3, 155.3; EI MS (rel int) 265 (parent, 15), 174 (100), 156 (30), 130 (32); HRMS calcd for $C_{17}H_{23}NO$ 257.1776, found 257.179 03.

5-Benzyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (63b) was prepared according to method G in 79% yield: mp 143–145 °C; ^{1}H-NMR (δ, $CDCl_3$) 1.72 (m, 1H), 2.2–2.4 (m, 3H), 2.31 (s, 3H), 2.89 (dd, J = 9, 13, 1H), 3.1–3.3 (m, 2H), 6.86 (s, 1H), 6.98 (d, J = 8, 1H), 7.1–7.3 (m, 6H), 8.73 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.8, 32.7, 34.6, 39.4, 39.7, 122.8, 126.2, 126.4, 126.6, 128.4, 129.0, 133.6, 137.1, 137.6, 140.0, 175.9; IR (KBr, cm^{-1}) 1671 (C=O); FAB MS (rel int) 265 (parent, 18), 174 (100), 146 (45), 132 (35). Anal. ($C_{18}H_{19}NO$) C, H, N.

3-Bromo-5-benzyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (64b) was prepared according to method A in 82% yield: mp 197–200 °C; ^{1}H-NMR (δ, $CDCl_3$) 2.2–2.3 (m, 1H), 2.32 (s, 3H), 2.48 (m, 1H), 2.86 (dd, J = 7, 12, 1H), 3.19 (dd, J = 5, 12, 1H), 4.47 (dd, J = 8, 11, 1H), 6.8–7.2 (m, 8H), 8.65 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.9, 38.7, 39.5, 40.1, 41.8, 44.2, 45.9, 46.9, 47.5, 123.2, 123.4, 125.9, 126.4, 126.5, 126.6, 127.1, 127.5, 128.5, 128.6, 128.8, 129.0, 132.7, 132.8, 136.3, 137.7, 138.9, 139.3, 169.3; IR (KBr, cm^{-1}) 1672 (C=O); FAB MS (rel int) 344/346 (parent, Br^{79}/Br^{81}, 46/44), 266 (70), 174 (56), 91 (100). Anal. ($C_{18}H_{18}BrNO\cdot{}^1/_4H_2O$) C, H, N.

***N-tert*-Butyl-2-(3-bromo-2-oxo-5-benzyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (65b)** was prepared according to method A, with crystallization of the crude reaction product from methylene chloride:isopropyl ether to give the more polar, *trans* isomer, mp 167–170 °C, in 52% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.32 (s, 9H), 2.18 (m, 1H), 2.32 (s, 3H), 2.51 (m, 1H), 2.88 (dd, J = 10, 12, 1H), 3.18 (dd, J = 5, 14, 1H), 3.50 (m, 1H), 4.28 (AB q, J_{AB} = 15, $\Delta\nu$ = 28, 2H), 4.443 (dd, J = 8, 12, 1H), 7.0–7.3 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 28.7, 38.3, 38.7, 47.1, 47.6, 51.5, 54.8, 124.0, 124.1, 125.4, 126.4, 128.4, 128.6, 128.9, 133.7, 138.0, 138.9, 141.2, 167.2, 168.3; IR (KBr, cm^{-1}) 3354 (NH), 1663 (C=O); FAB MS (rel int) 457/459 (parent, Br^{79}/Br^{81}, 9/8), 306 (62), 278 (53), 91 (100). Anal. ($C_{24}H_{29}BrN_2O_2\cdot{}^1/_4H_2O$) C, H, N.

***N-tert*-Butyl-2-(3-azido-2-oxo-5-benzyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (66b)** was prepared according to method A in 70% yield as a solid, mp 169–172 °C, *cis* isomer: ^{1}H-NMR (δ, $CDCl_3$) 1.38 (s, 9H), 2.16 (t, J = 13, 1H), 2.30 (s, 3H), 2.50 (m, 1H), 2.77 (d, J = 8, 2H), 3.10 (m, 1H), 3.91 (dd, J = 7, 12, 1H), 4.26 (AB q, J_{AB} = 14, $\Delta\nu$ = 350, 2H), 6.40 (bs, 1H), 6.8–7.3 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 21.1, 28.7, 38.0, 41.2, 43.0, 51.6, 55.5, 58.4, 125.3, 125.4, 126.4, 128.1, 128.5, 128.6, 129.1, 130.6, 133.2, 139.0, 140.5, 167.4, 171.3; IR (KBr, cm^{-1}) 2107 (N_3), 1666 (C=O); FAB MS (rel int) 420 (parent + 1, 84), 394 (85), 347 (52), 155 (45), 119 (100). Anal. ($C_{24}H_{29}N_5O_2\cdot{}^1/_4H_2O$) C, H, N.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-benzyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (67b)** was prepared according to method A, mp 155–165 °C, in approximately 100% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.34 (s, 9H), 2.00 (m, 1H), 2.23 (s, 3H), 2.62 (m, 1H), 2.72 (d, J = 8, 2H), 3.02 (m, 1H), 4.2–4.4 (m, 3H), 4.23 (AB q, J_{AB} = 15, $\Delta\nu$ = 330, 2H), 6.62 (bs, 1H), 6.7–7.2 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 28.7, 40.6, 41.4, 43.3, 50.8, 51.7, 54.7, 124.9, 126.2, 127.9, 128.3, 129.1, 130.8, 133.6, 138.6, 139.6, 140.5, 167.7, 173.7; IR (KBr, cm^{-1}) 1664 (C=O); FAB MS (rel int) 394 (parent + 1, 100), 321 (98), 144 (50); HRMS calcd for $C_{24}H_{31}N_3O_2$ 393.2409, found 393.244 27.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-benzyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (68b)** was prepared according to method A as a white solid, mp 298–315 °C, in 80% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.41 (s, 9H), 1.97 (t, J = 13, 1H), 2.32 (s, 3H), 2.5–2.8 (m, 3H), 3.18 (m, 1H), 4.46 (AB q, J_{AB} = 16, $\Delta\nu$ = 288, 2H), 4.58 (dd, J = 7, 12, 1H), 6.8–7.4 (m, 15H); ^{13}C-NMR (δ, $CDCl_3$) 20.8, 22.9, 28.3, 38.6, 41.4, 42.7, 50.7, 53.2, 54.7, 122.4, 124.4, 125.8, 126.4, 126.7, 128.6, 128.7, 128.9, 129.3, 130.5, 130.7, 131.2, 133.3, 135.2, 137.5, 138.6, 139.2, 139.6, 156.7, 169.0, 174.9; IR (KBr, cm^{-1}) 1645, 1661, 1684 (C=O); FAB MS (rel int) 547 (parent + 1, 19), 474 (15), 309 (15), 155 (53), 135 (34), 119 (100), 103 (46). Anal. ($C_{31}H_{35}ClN_4O_3\cdot{}^1/_2H_2O$) C, H, N.

Preparation of *N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)-ureido)-2-oxo-5-isopropyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (68c). 4-Isopropyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one oxime (62c) was prepared from 4-isopropyl-7-methyl-1,2,3,4-tetrahydronaphth-1-one, **61c**, according to method C in 100% yield: mp 90–92 °C; ^{1}H-NMR (δ, $CDCl_3$) 0.83 (d, J = 7, 3H), 0.99 (d, J = 7, 3H), 1.70 (m, 2H), 2.08 (m, 1H), 2.33 (s, 3H), 2.78 (m, 3H), 7.02 (m, 2H), 7.64 (s, 1H), 9.46 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.6, 21.2, 21.7, 23.0, 29.7, 45.7, 124.9, 125.0, 129.2, 129.7, 136.0, 140.5, 155.8; FAB MS (rel int) 217 (parent, 25), 174 (100), 130 (45). Anal. ($C_{14}H_{19}NO$) C, H, N.

5-Isopropyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (63c) was prepared according to method G in 56% yield: mp 141.5–143.5 °C; ^{1}H-NMR (δ, $CDCl_3$) 0.76 (d, J = 6, 3H), 1.01 (d, J = 6, 3H), 1.78 (m, 1H), 2.0–2.5 (m, 5H), 2.29 (s, 3H), 6.81 (bs, 1H), 6.93 (d, J = 8, 1H), 7.08 (d, J = 8, 1H), 8.58 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.8, 20.9, 22.4, 29.3, 32.3, 32.8, 46.6, 122.9, 126.2, 128.2, 133.5, 136.7, 137.9, 176.1; IR (KBr, cm^{-1}) 1673 (C=O); FAB MS (rel int) 217 (parent, 20), 174 (100), 146 (40), 132 (35). Anal. ($C_{14}H_{19}NO\cdot{}^1/_8H_2O$) C, H, N.

3-Bromo-5-isopropyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (64c) was prepared according to method A in 85% yield as a mixture of diastereomers: mp 138–143 °C; ^{1}H-NMR (δ, $CDCl_3$) 0.52, 0.87, 0.98, and 1.04 (d's, J = 7, 6H), 2.0–2.9 (multiplets, 4H), 2.30 (s, 3H), 4.37 (dd, J = 8, 12) and 4.62 (dd, J = 7, 11, 1H), 6.8–7.2 (m, 3H), 8.4–8.7 (m, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.4, 20.8, 21.5, 21.8, 22.1, 28.6, 30.3, 43.1, 45.4, 47.1, 48.0, 49.8, 123.6, 123.7, 126.7, 127.0, 127.3, 131.1, 132.4, 132.5, 132.6, 135.8, 136.9, 137.2, 137.9, 169.6, 170.1; IR (KBr, cm^{-1}) 1685 (C=O); FAB MS (rel int) 296/298 (parent, Br^{79}/Br^{81}, 65/62), 218 (100), 174 (51). Anal. ($C_{14}H_{18}BrNO$) C, H, N.

***N-tert*-Butyl-2-(3-bromo-2-oxo-5-isopropyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (65c)** was prepared according to method A, with chromatographic separation of the diastereomers on silica gel using hexane:ethyl acetate as eluant, giving the less polar, *cis* isomer, mp 176–179 °C, in 35% yield, and the more polar, *trans* isomer, mp 161–164 °C, 51% yield, which was used in the next step. Spectra for *trans* isomer: ^{1}H-NMR (δ, $CDCl_3$) 0.88 (d, J = 7, 3H), 1.02 (d, J = 7, 3H), 1.31 (s, 9H), 2.11 (m, 2H), 2.30 (s, 3H), 2.6 (m, 2H), 4.26 (m, 2H), 4.3 (m, 1H), 6.23 (bs, 1H), 7.0–7.2 (m, 3H); ^{13}C-NMR (δ, $CDCl_3$) 20.5, 21.0, 21.9, 28.3, 28.4, 28.7, 45.0, 46.0, 48.0, 51.4, 54.8, 124.2, 126.0, 128.4, 133.3, 137.7, 141.6, 167.2, 168.6; IR (KBr, cm^{-1}) 3347 (NH), 1663 (C=O); FAB MS (rel int) 409/411 (parent, Br^{79}/Br^{81}, 52/48), 336/338 (Br^{79}/Br^{81}, 90/85), 331 (75), 258 (100), 230 (73), 144 (50). Anal. ($C_{20}H_{29}BrN_2O_2\cdot{}^1/_4H_2O$) C, H, N.

***N-tert*-Butyl-2-(3-azido-2-oxo-5-isopropyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (*cis* isomer 66c)** was prepared according to method A from the *trans* bromide in 74.5% yield: mp 157–159 °C; ^{1}H-NMR (δ, $CDCl_3$) 0.43 (d, J = 7, 3H), 0.98 (d, J = 7, 3H), 1.35 (s, 9H), 1.78 (m, 1H), 2.2–2.4 (m, 2H), 2.30 (s, 3H), 2.50 (m, 1H), 3.87 (dd, J = 7, 12, 1H), 4.09 (AB q, J_{AB} = 14, $\Delta\nu$ = 340, 2H), 6.35 (bs, 1H), 6.92 (bs, 2H), 7.23 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 21.8, 21.9, 28.6, 30.7, 37.2, 48.8, 51.4, 55.2, 58.6,

125.1, 128.0, 131.2, 133.7, 138.7, 140.3, 167.6, 171.0; IR (KBr, cm^{-1}) 2104 (N_3), 1670 broad (C=O); FAB MS (rel int) 372 (parent + 1, 54), 346 (100), 299 (65), 273 (52), 144 (71). Anal. ($C_{20}H_{29}N_5O_2 \cdot {}^1/_4H_2O$) C, H, N.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-isopropyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide (67c)** was prepared according to method A in 100% yield as a foam, mp 100–120 °C; ^{1}H-NMR (δ, $CDCl_3$) 0.40 (d, J = 7, 3H), 0.93 (d, J = 7, 3H), 1.20 (m, 1H), 1.33 (s, 9H), 1.60 (m, 1H), 2.00 (m, 1H), 2.27 (s, 3H), 2.56 (m, 1H), 3.68 (m, 3H), 4.09 (AB q, J_{AB} = 15, $\Delta\nu$ = 377, 2H), 6.47 (bs, 1H), 6.90 (m, 2H), 7.10 (s, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 21.9, 22.0, 28.5, 28.7, 30.7, 40.2, 49.3, 50.8, 51.5, 54.6, 124.7, 127.7, 127.8, 131.3, 134.3, 138.2, 140.4, 167.9, 174.5; IR (KBr, cm^{-1}) 1668 (C=O); FAB MS (rel int) 346 (parent + 1, 100), 330 (65), 273 (93); HRMS calcd for $C_{20}H_{31}N_3O_2$ 345.2416, found 345.239 82.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-isopropyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (68c)** was prepared according to method A in 59% yield: mp 272–275 °C; ^{1}H-NMR (δ, $CDCl_3$) 0.41 (d, J = 7, 3H), 0.94 (d, J = 7, 3H), 1.35 (s, 9H), 1.60 (m, 1H), 1.99 (t, J = 7, 1H), 2.27 (s, 3H), 2.31 (m, 1H), 2.52 (m, 1H), 4.12 (AB q, J_{AB} = 16, $\Delta\nu$ = 379, 2H), 4.40 (dd, J = 7, 12, 1H), 6.8–7.0 (7H); ^{13}C-NMR (δ, $CDCl_3$) 20.9, 21.8, 28.5, 30.7, 37.5, 49.0, 49.3, 49.6, 50.4, 51.8, 54.0, 116.5, 118.6, 122.1, 123.9, 128.0, 129.5, 131.6, 131.7, 133.8, 134.3, 138.5, 140.2, 140.5, 155.1, 167.8, 174.4; IR (KBr, cm^{-1}) 1660, 1670, 1687 (C=O); FAB MS (rel int) 500 (parent + 1, 37), 426 (37), 273 (30), 132 (37), 119 (50), 108 (90), 91 (100). Anal. ($C_{27}H_{35}ClN_4O_3 \cdot {}^2/_3H_2O$) C, H, N.

Preparation of *N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-(4-tolyl)-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (78). 4,4-Di(4-tolyl)but-3-enoic acid (69) was prepared according to method C in 66% yield, R_f = 0.25 in 5% methanol/methylene chloride. This material was used directly in the next step.

4,4-Di(4-tolyl)butanoic Acid (70). The oil from the preceding step was treated according to method C to afford an oil in 75% yield: ^{1}H-NMR (δ, $CDCl_3$) 2.32 (s, 6H), 2.3–2.5 (m, 4H), 3.90 (m, 1H), 7.0–7.2 (m, 8H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 30.4, 32.6, 49.6, 127.7, 129.3, 135.8, 141.3, 180.1; IR (cm^{-1}, KBr) 1706 (C=O); MS (rel int) 268 (parent, 10), 195 (100), 165 (30); HRMS calcd for $C_{18}H_{20}O_2$ 268.1458, found 268.144 45.

4-(4-Tolyl)-7-methyl-1,2,3,4-tetrahydronaphth-1-one (71) was prepared according to method C to afford the product as a solid, mp 90–92 °C, in 49% yield: ^{1}H-NMR (δ, $CDCl_3$) 2.2–2.4 (m, 2H), 2.33 (s, 3H), 2.36 (s, 3H), 2.5–2.7 (m, 2H), 4.18 (m, 1H), 6.8–7.2 (m's, 6H), 7.91 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.98, 21.03, 32.0, 36.8, 44.6, 127.2, 127.3, 128.5, 129.3, 129.5, 132.6, 134.6, 136.3, 136.7, 140.9, 143.7, 198.5; IR (cm^{-1}, KBr) 1685 (C=O); MS (rel int) 250 (parent, 100), 222 (45), 208 (54), 207 (55), 178 (45). Anal. ($C_{18}H_{20}O$) C, H.

4-(4-Tolyl)-7-methyl-1,2,3,4-tetrahydronaphth-1-one oxime (72) was prepared according to method C: mp 174–177 °C; yield 74%; ^{1}H-NMR (δ, $CDCl_3$) 2.0–2.2 (m, 2H), 2.34 (s, 3H), 2.36 (s, 3H), 2.84 (t, J = 7, 2H), 4.08 (m, 1H), 6.85 (d, J = 7, 1H), 6.9–7.1 (m, 5H), 7.81 (bs, 1H), 9.36 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 21.2, 21.4, 29.7, 44.4, 124.2, 128.4, 129.2, 130.5, 135.9, 136.4, 139.1, 141.1, 155.5; MS (rel int) 265 (parent, 100), 248 (40), 156 (35). Anal. ($C_{18}H_{19}NO$) C, H, N.

5-(4-Tolyl)-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (73) was prepared according to method G: mp 218–220 °C; yield 73%; ^{1}H-NMR (δ, $CDCl_3$) 2.28 (s, 3H), 2.35 (s, 3H), 2.4–2.6 (m, 4H), 4.33 (m, 1H), 6.65 (d, J = 8, 1H), 6.81 (d, J = 8, 1H), 6.88 (s, 1H), 7.17 (bs, 4H), 8.86 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.8, 21.1, 32.9, 34.0, 44.4, 122.4, 126.2, 128.5, 128.8, 129.3, 133.9, 136.5, 137.1, 137.2, 138.2, 175.7; IR (cm^{-1}, KBr) 1675 (C=O); MS (rel int) 265 (parent, 100), 222 (60), 210 (80), 208 (55). Anal. ($C_{18}H_{19}NO$) C, H, N.

3-Bromo-5-(4-tolyl)-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (74) was prepared according to method A: mp 195–201 °C; 87% yield; ^{1}H-NMR (δ, $CDCl_3$) 2.29 (s, 3H), 2.36 (s, 3H), 2.83 (m, 1H), 3.04 (m, 1H), 4.40 (m, 1H), 4.63 (dd, J = 8, 12, 1H), 6.63 (d, J = 8, 1H), 6.85 (d, J = 8, 1H), 6.94 (s, 1H), 7.17 (m, 4H), 8.93 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.8, 21.1, 44.4, 46.2, 47.3, 123.2, 127.2, 128.2, 128.7, 129.5, 133.2, 135.9, 136.4, 137.1, 137.7, 169.4; IR (cm^{-1}, KBr) 1690 (C=O); MS (rel int) 344/346 (parent, Br^{79}/Br^{81}, 100/97), 264 (75), 210 (28), 105 (23). Anal. ($C_{18}H_{18}NOBr \cdot {}^1/_2H_2O$) C, H, N.

***N-tert*-Butyl-2-[3-bromo-2-oxo-5-(4-tolyl)-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (75)** was prepared according to method A, mp 181–183 °C, 63% yield of the more polar, *trans* isomer diastereomer, after separation by column chromatography: ^{1}H-NMR (δ, $CDCl_3$) 1.34 (s, 9H), 2.29 (s, 3H), 2.34 (s, 3H), 2.80 (m, 1H), 2.95 (m, 1H), 4.34 (bs, 2H), 4.52 (m, 2H), 6.11 (bs, 1H), 6.57 (d, J = 8, 1H), 6.88 (d, J = 8, 1H), 7.12 (s, 1H), 7.15 (bs, 4H); ^{13}C-NMR (δ, $CDCl_3$) 21.0, 21.1, 28.7, 43.4, 45.8, 47.2, 51.5, 55.0, 123.7, 127.6, 128.2, 128.6, 129.4, 134.7, 136.1, 137.0, 138.1, 140.7, 167.1, 169.4; IR (cm^{-1}, KBr) 1660, 1680 (C=O); FAB MS (rel int) 457/459 (parent, Br^{79}/Br^{81}, 28/29), 384/386 (Br^{79}/Br^{81}, 84/80), 304/306 (Br^{79}/Br^{81}, 61/52), 276 (100), 105 (81). Anal. ($C_{24}H_{29}N_2O_2Br$) C, H, N.

***N-tert*-Butyl-2-[3-azido-2-oxo-5-(4-tolyl)-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (76)** was prepared according to method A: mp 195–196.5 °C; 49%; ^{1}H-NMR (δ, $CDCl_3$) 1.29 (s, 9H), 2.25 (s, 3H), 2.34 (s, 3H), 2.72 (m, 1H), 2.88 (m, 1H), 3.10 (AB q, J_{AB} = 15, $\Delta\nu$ = 288, 2H), 3.91 (m, 1H), 4.10 (m, 1H), 6.17 (bs, 1H), 6.8–7.2 (m, 7H); ^{13}C-NMR (δ, $CDCl_3$) 20.9, 21.1, 28.6, 35.8, 43.0, 51.3, 54.8, 58.4, 125.9, 126.1, 126.2, 126.3, 128.4, 129.1, 129.3, 130.0, 130.1, 134.9, 136.0, 138.1, 139.2, 140.9, 168.0, 170.1; IR (cm^{-1}, KBr) 2110 (N_3), 1660, 1700 (C=O); FAB MS (rel int) 420 (parent + 1, 33), 392 (64), 347 (70), 321 (54), 234 (51), 222 (83), 144 (48), 105 (100). Anal. ($C_{24}H_{29}N_5O_2$) C, H, N.

***N-tert*-Butyl-2-[3-amino-2-oxo-5-(4-tolyl)-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (77)** was prepared according to method A: mp 273–276 °C; 31% yield; ^{1}H-NMR (δ, $CDCl_3$) 1.24 (s, 9H), 2.18 (s, 3H), 2.28 (s, 3H), 3.0 (m, 2H), 3.15 (AB q, J_{AB} = 16, $\Delta\nu$ = 252, 2H), 3.92 (t, J = 10, 1H), 4.11 (m, 1H), 6.44 (bs, 1H), 6.8–7.2 (m, 7H); ^{13}C-NMR (δ, $CDCl_3$) 20.7, 21.0, 28.4, 34.6, 42.9, 49.9, 51.7, 53.3, 125.5, 126.0, 128.6, 129.0, 130.6, 134.6, 136.0, 137.9, 139.3, 140.0, 167.9, 168.7; IR (cm^{-1}, KBr) 1650, 1680 (C=O); FAB MS (rel int) 394 (parent + 1, 100), 321 (98), 222 (54), 105 (44). Anal. ($C_{24}H_{31}N_3O_2 \cdot H_2CO_3$) C, H, N.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-(4-tolyl)-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide (78)** was prepared according to method A, mp 239–241 °C from benzene, 92% yield: ^{1}H-NMR (δ, $CDCl_3$) 1.31 (s, 9H), 2.22 (s, 3H), 2.35 (s, 3H), 2.91 (m, 2H), 3.43 (AB q, J_{AB} = 16, $\Delta\nu$ = 298, 2H), 4.20 (m, 1H), 4.60 (m, 1H), 6.64 (d, J = 7, 1H), 6.8–7.3 (m, 10H), 7.55 (bs, 1H), 7.93 (bs, 1H); ^{13}C-NMR (δ, $CDCl_3$) 20.9, 21.2, 28.6, 36.9, 43.7, 50.5, 51.9, 53.2, 116.9, 119.0, 122.1, 124.8, 126.1, 128.4, 129.0, 129.5, 130.7, 134.3, 135.1, 136.0, 138.8, 139.0, 140.6, 140.8, 155.2, 167.4, 173.6; IR (cm^{-1}, KBr) 1660, 1700 (C=O); FAB MS (rel int) 547 (parent + 1, 20), 474 (70), 321 (40), 248 (74), 222 (100), 131 (44), 105 (68). Anal. ($C_{31}H_{35}ClN_4O_3 \cdot C_6H_6$) C, H, N.

Preparation of 4 and 82: *N-tert*-Butyl-2-[3-(L-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropionamido)-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (79). To a 125 mL round-bottomed flask equipped with N_2 inlet were added 1.00 g (2.64 mmol) of *N-tert*-butyl-2-(3-amino-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide, **42a**, 0.70 g (2.64 mmol) of *t*-BOC-L-phenylalanine, 0.404 g (2.64 mmol) of *N*-hydroxybenzotriazole, 0.506 g (2.64 mmol) of ethyl[(dimethylamino)propyl]carbodiimide hydrochloride, and 0.662 mL (4.75 mmol) of triethylamine. The reaction mixture was stirred at room temperature for 14 h (TLC R_f = 0.35/0.32 for the diastereomers in 1:1 ethyl acetate:hexane), taken up in ethyl acetate, washed with water, 1 N hydrochloric acid, water, aqueous saturated sodium bicarbonate solution, water, and brine, dried over sodium sulfate, and evaporated to a foam, suitable for further use, 1.60 g (97%): ^{1}H-NMR (δ, $CDCl_3$) 1.26, 1.31 (s's, 9H), 1.373, 1.379 (s's, 9H), 2.30, 2.34 (s's, 3H), 2.8–3.1 (m, 5H), 3.03 (AB q, J_{AB} = 15, $\Delta\nu$ = 275) and 3.19 (AB q, J_{AB} = 16, $\Delta\nu$ = 294, 2H), 3.4–3.5 (m, 2H), 5.1, 5.4, and 5.9 (m's, N*H*, 3H), 6.7–

7.4 (m, 13H); FAB MS (rel int) 627 (parent + 1, 19), 527 (100), 498 (61), 454 (76), 234 (77), 208 (82), 120 (64).

***N-tert*-Butyl-2-[3-(L-2-amino-3-phenylpropionamido)-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic Acid Amide (80a and 80b).** To a 125 mL round-bottomed flask equipped with a N_2 inlet were added the above foam and 40 mL of ethyl acetate. The solution was cooled to 0 °C, saturated with HCl gas, stirred at 0 °C, allowing to warm to room temperature over 2.5 h (TLC indicates no starting material, products at $R_f = 0.3$ and 0.2 in 5% aqueous acetonitrile), and then poured into a large flask containing aqueous bicarbonate solution. The organic layer was washed with further bicarbonate and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using 3% aqueous acetonitrile as eluant (20 mL fractions, fractions 29–55 contain one diastereomer, fractions 56, 57 mixed, fractions 58–160 contain the other) to afford each diastereomer as an oil/foam.

Less polar diastereomer 80a: 618 mg (46%); $\alpha_D = -71.8$; ^{1}H-NMR (δ, $CDCl_3$) 1.27 (s, 9H), 1.40 (bs, 2H), 2.30 (s, 3H), 2.52 (m, 1H), 2.68 (dd, $J = 9, 16$, 1H), 2.92 (m, 1H), 3.05 (AB q, $J_{AB} = 16$, $\Delta\nu = 302$, 2H), 3.11 (dd, $J = 3.5, 12$, 1H), 3.53 (m, 1H), 4.10 (m, 1H), 4.52 (m, 1H), 5.99 (s, 1H), 6.9–7.4 (m, 13H), 8.11 (d, $J = 7$, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.1, 28.6, 36.6, 40.9, 43.8, 48.9, 51.2, 53.8, 56.2, 125.8, 126.3, 126.8, 128.2, 128.4, 128.6, 129.4, 130.4, 135.1, 137.7, 138.9, 140.9, 142.0, 167.9, 171.1, 173.7.

More polar diastereomer 80b: 590 mg (44%); $\alpha_D = +46.3$; ^{1}H-NMR (δ, $CDCl_3$) 1.24 (s, 9H), 1.40 (bs, 2H), 2.26 (s, 3H), 2.58 (m, 2H), 2.95 (m, 1H), 3.07 (AB q, $J_{AB} = 16$, $\Delta\nu = 299$, 2H), 3.17 (dd, $J = 4, 13$, 1H), 3.55 (m, 1H), 4.13 (m, 1H), 4.53 (m, 1H), 5.99 (s, 1H), 6.9–7.4 (m, 13H), 7.89 (d, $J = 7$, 1H); ^{13}C-NMR (δ, $CDCl_3$) 21.1, 28.6, 36.3, 41.1, 43.8, 49.0, 51.3, 53.9, 56.7, 125.7, 126.3, 126.7, 128.3, 128.4, 128.7, 129.3, 130.4, 135.1, 138.1, 139.0, 140.9, 141.9, 167.9, 171.1, 174.0.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic Acid Amide [(−)-Diastereomer 81a].** To a 100 mL round-bottomed flask equipped with a condenser and N_2 inlet were added 618 mg (1.17 mmol) of the less polar diastereomer of **80a**, 10 mL of 1,2-dichloroethane, and 0.148 mL (1.23 mmol) of phenyl isothiocyanate. The solution was refluxed for 1.2 h, cooled, and evaporated. The residue (major product $R_f = 0.3$ in 1:1 ethyl acetate:hexane) was taken up in 10 mL of trifluoroacetic acid, heated at 60 °C for 50 min (TLC, $R_f = 0.3$ for product in 10% methanol in methylene chloride), cooled, and evaporated. The residue was taken up in ethyl acetate, washed with aqueous sodium bicarbonate solution, and then extracted into 2 × 50 mL of 1 N hydrochloric acid. The acid layer was washed with ethyl acetate, the pH adjusted to 8 with sodium carbonate, and extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to a foam, suitable for further use: 282 mg (64%); $\alpha_D = -131.4$. Spectral data matched that of the racemate, **42a**.

***N-tert*-Butyl-2-(3-amino-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid amide [(+)-diastereomer 81b]** was prepared as above in 63% yield; $\alpha_D = +138.0$. Spectral data matched that of the racemate, **42a**.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide [(−)-diastereomer 82]** was prepared as for the racemate in 83% yield, mp 130–155 °C, as a solidified oil from isopropyl ether and cyclohexane, $\alpha_D = -107.7$. Spectral data matched those of the racemate, **43a**.

***N-tert*-Butyl-2-[3-(3-(3-chlorophenyl)ureido)-2-oxo-5-phenyl-8-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]ethanoic acid amide [(+)-diastereomer 4]** was prepared as for the racemate in 81% yield, mp 145–160 °C, as a solidified oil from methylene chloride and cyclohexane, $\alpha_D = +107.4$. Spectral data matched those of the racemate, **43a**.

CCK-B Binding Assay. The tissue for the assay was prepared by dissecting the cortex from a male Hartley guinea pig and homogenizing 15 strokes with a Teflon homogenizer in 20 volumes of 50 mM Tris-HCl, pH 7.4, with 5 mM $MnCl_2$ at 4 °C. The homogenate was centrifuged at 4 °C for 30 min at 100000*g*. The pellet was resuspended in the same buffer and centrifuged as before. The final pellet was diluted to a concentration of 10 mg/mL with assay buffer and kept refrigerated.

The buffer for the assay consisted of 10 mM HEPES, 5 mM $MgCl_2$, 1 mM EGTA, 130 mM NaCl, 0.2 mg/mL bacitracin, at pH 6.5 and room temperature, with 0.5 mg/mL bovine serum albumin added before incubation was begun. The test drugs were made up at 1 mM in 100% dimethyl sulfoxide (DMSO) and diluted to test concentration using 4% DMSO so as to give a concentration of 1% DMSO in the final assay mixture. The incubation mixture consisted of 50 μL of tissue preparation, 100 μL of a solution of [^{125}I]BH-CCK-8 (NEX 203, 2200 Ci/mmol) at 50 pM, 20 μL of the test drug solution (or a 1 μM solution of CI-988, the standard CCK-B antagonist L-365,260[39] as a blank, or vehicle as a control), and 30 μL of the assay buffer with 4% DMSO. The incubation was initiated by adding tissue preparation and continued at room temperature for 2 h. It was then terminated by spinning the plate containing the incubation in a H1000B rotor fitted on a Sorvall RT6000 refrigerated centrifuge at 4 °C for 5 min at 3000 rpm. The supernatant was discarded, and the pellet was washed with 200 μL of wash buffer and then recentrifuged. The supernatant was again decanted, and the pellet was harvested onto Betaplate filters which had been soaked in 0.2% polyethylenimine for a minimum of 2 h, using a Skatron cell harvester at setting 222 using 50 mM Tris-HCl, pH 7.4, as the wash buffer. The filtermats were counted on a Betaplate counter for 45 s per sample. Data were analyzed and results are reported as IC_{50} values based on six concentrations done in at least three separate experiments.

CCK-A Binding Assay. The tissue for the assay was prepared by dissecting the pancreas from a male Hartley guinea pig and placing it in saline. The fatty tissue and blood vessels were dissected away, and the tissue was placed in 20 volumes of tissue buffer (50 mM Tris-HCl, pH 7.4, 0.35 mg/mL bacitracin, and 0.5 mg/mL soybean trypsin inhibitor) at 4 °C and minced using scissors. The tissue was homogenized using a Polytron at setting 9 for two 15 s bursts, poured through several layers of gauze, and centrifuged twice at 4 °C for 15 min at 100000*g* (the pellet was resuspended in 20 volumes of tissue buffer with the Polytron between spins). The final pellet was diluted to a concentration of 1.25 mg/mL in tissue buffer for use in the assay.

The buffer for the assay consisted of 50 mM Tris-HCl, pH 7.4, 8.3 mM $MgCl_2$, and 8.3 mM dithiothreitol. The test drugs were made up at 1 mM in 100% dimethyl sulfoxide (DMSO) and diluted to test concentration using 4% DMSO so as to give a concentration of 1% DMSO in the final assay mixture. The incubation mixture consisted of 100 μL of tissue preparation, 100 μL of a solution of [^{125}I]BH-CCK-8 (NEX 203, 2200 Ci/mmol) at 60 pM, 25 μL of the test drug solution (or a 1 μM solution of L-364,718, a standard CCK-A antagonist,[1] as a blank, or vehicle as a control), and 25 μL of binding buffer with 4% DMSO. The incubation was initiated by adding tissue, carried out for 30 min at 37 °C, and then terminated by rapid filtration onto GF/B filters which had been precut to fit a Skatron harvester and soaked in a wash buffer (50 mM Tris-HCl, pH 7.4, and 0.1 mg/mL bovine serum albumin at 4 °C) for at least 2 h, using a Skatron cell harvester at setting 555. The filtermats were counted on a Betaplate counter for 45 s per sample. Data were analyzed, and results are reported as IC_{50} values based on six concentrations done in at least three separate experiments.

Pentagastrin-Induced Acid Secretion Assay. Gastric acid secretion studies were conducted in rats using a modification of the pylorus ligation model described previously.[40] Fasted male Sprague–Dawley rats (125–250 g) were anesthetized by inhalation with methoxyflurane (Metofane, Pitman-Moore, Inc., Chicago, IL), and the pylorus was ligated. Compounds were administered in a vehicle of DMSO:emulphor:saline (5:15:80, v/v/v) by subcutaneous injection (4 μL/kg). Pentagastrin was administered in a vehicle of DMSO:saline (0.01:99.99, v/v). Rats were sacrificed 2 h after administration of drugs and pentagastrin, and the gastric fluid was collected and clarified by centrifugation. Samples of

gastric fluid were diluted with H_2O and titrated to pH 7.0 with 0.1 N NaOH using a Radiometer TTT85 titrator and an ABU80 autoburette (Radiometer America, Inc., Westlake, OH). The amount of NaOH used was taken as a direct measure of the titratable acid (expressed in microequivalents) in the sample. The acid content was calculated per milliliter of gastric fluid and normalized to the time of the ligation and the body weight of the rat. Statistical differences between treatment groups were determined using a Student's *t* test.

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Supplementary Material Available: Parameters, atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and H-atom coordinates from single X-ray crystal data for the compounds in Figure 2 and compounds **28** and **29a** (31 pages). Ordering information is given on any current masthead page.

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