(200 MHz, DMSO-d_6) δ 2.57 (s, 3, CH_3CO), 3.57 (m, 2, CH_2NH), 3.80 (dd (J = 9.0, 6.5 Hz), 1, C-4 H trans to C-5 H), 4.22 (dd (J = 9.0, 9.0 Hz), 1, C-4 H cis to C-5 H), 4.83 (m, 1, C-5 H), 6.50 (s, 1, $CHCl_2CON$), 7.67 and 8.00 (AB (J_{AB} = 10 Hz), 4, aryl H), and 9.00 (m, 1, NH). Anal. ($C_{14}H_{14}N_2O_4Cl$) C, H, N, Cl.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-(acetylamino)acetamide (57). A. (*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]chloroacetamide. Via the general Schotten-Baumann procedure described for preparation of **10**, 7.47 g (28 mol) of **22** and 9.43 g of chloroacetic anhydride yielded 7.9 g (92%) of the title compound, mp 171–172 °C (THF/water).

B. (*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-azidoacetamide. By the general azide displacement procedure described for preparation of **8**, 3.10 g (10 mmol) of the chloroacetamide from part A yielded 2.75 g (87%) of the title azide, mp 143.5–144 °C.

C. (*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-aminoacetamide Hydrochloride. By the general reduction procedure described for the preparation of **9**, 2.5 g (7.8 mmol) of the azidoacetyl compound described in part B afforded 1.2 g (47%) of the title amine hydrochloride, mp >250 °C.

D. (*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-(acetylamino)acetamide (57). By the general Schotten-Baumann acetylation procedure described for the preparation of **10**, 0.500 g (1.5 mmol) of the amide hydrochloride described in part C above yielded 0.360 g (71%) of **57**, mp 234–235 °C (acetonitrile/ether). Anal. ($C_{16}H_{19}N_3O_5$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-3-oxobutanamide (58). By the general Schotten-Baumann acylation procedure described for the preparation of **10**, 6.17 g (0.023 mol) of **22** and 2.2 mL of diketene afforded 3.99 g (54%) of **58**, mp 160–161 °C (acetonitrile). Anal. ($C_{16}H_{18}N_2O_5$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-cyanoacetamide (59). By the general displacement procedure described for **8**, 2.1 g (0.0068 mol) of (*S*)-*N*-[[3-(4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]chloroacetamide, prepared as described in the preparation of **57**, and 0.500 g of potassium cyanide yielded 1.40 g (68%) of **59**, mp 169–170 °C (20:1 ethanol/acetonitrile). Anal. ($C_{15}H_{15}N_3O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-thiocyanoacetamide (60). By the general displacement procedure described for **8**, 2.1 g (0.0068 mol) of (*S*)-*N*-[[3-(4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]chlorothioacetamide, prepared as described in the preparation of **57**, and 0.700 g of potassium cyanide yielded 1.70 g (75%) of **60**, mp 144 °C dec (ethanol). Anal. ($C_{15}H_{15}N_3O_4S$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-methoxyacetamide (61). By the general Schotten-Baumann procedure described for **10**, 1.4 g (5 mmol) of **22** and 0.43 mL of methoxyacetyl chloride yielded 1.10 g (69%) of **61**, mp 155.5–157 °C (acetonitrile). Anal. ($C_{15}H_{18}N_2O_5$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]urea (62). To 2.00 g (0.007 mol) of **22** free base in 100 mL of glyme was added 1.3 g of phenyl carbamate, and the mixture was refluxed under nitrogen for 3.0 h. The solution was then cooled, concentrated in vacuo, and diluted with ether and filtered: 1.98 g (84%); mp 180.5–182 °C (acetonitrile). Anal. ($C_{12}H_{15}N_3O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-*N'*,*N'*-dimethylurea (63). By the general Schotten-Baumann procedure described for **10**, 1.4 g (5 mmol) of **22** and 0.51 mL of *N*,*N*-dimethylcarbamoyl chloride yielded 0.400 g (25%) of **63**, mp 203–205 °C dec (acetonitrile). Anal. ($C_{15}H_{19}N_3O_4$) C, H, N.

In Vitro Susceptibility Tests. MICs of the compounds for the various bacterial strains were determined by a microtiter broth dilution assay.[2,14] For comparative purposes, MICs of racemic compounds were divided by 2 to reflect the fact that only one oxazolidinone enantiomer possesses antibacterial activity.

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Cholecystokinin Antagonists. Synthesis and Biological Evaluation of 3-Substituted Benzolactams

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A series of 1,3-substituted benzolactams are reported that are potent nonpeptidal antagonists of the peptide hormone cholecystokinin (CCK). Design considerations were based upon the natural product CCK antagonist asperlicin and the potent benzodiazepine antagonist series exemplified by L-364,718 (1). Compound **19**, the most potent compound in the benzolactam series, had an IC_{50} = 3 nM for inhibition of binding of ^{125}I-CCK-8 to CCK receptors in rat pancreatic tissue, and its racemic analogue **8** was found to be orally active in inhibiting CCK-induced gastric emptying in mice, with an ED_{50} = 2.6 mg/kg po. The effects of ring size, substitution at positions 1 and 3, and stereochemistry at position 3 are discussed. Conformational studies of compound **19** and L-364,718 have delineated similarities that these molecules share in their core conformations and substituent orientations.

The peptide cholecystokinin (CCK) is a hormone and proposed neutrotransmitter found in gut and brain. This peptide has been reported to stimulate pancreatic and biliary secretion, produce gall bladder contraction, increase gut motility, induce satiety, and antagonize the analgesic effects of opiates.[1-3] The search for CCK antagonists has accelerated in recent years to produce agents useful in clarifying these various roles of CCK in physiology and to provide possible therapeutic applications. Several years ago the isolation and properties of the natural product CCK antagonist asperlicin were announced.[4] It is a se-

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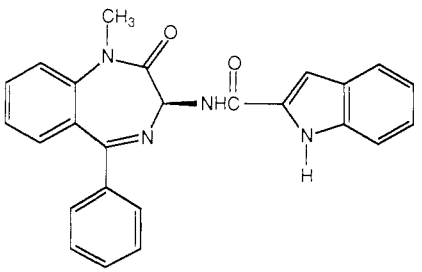
Table I. Physical and Receptor Binding Data for Compounds of Structure V

no.	R	R_1	n	stereo	mp, °C	formula[a]	IC_{50}, μM[b]
1 (L-364, 718)							0.0008[c]
2	CH_2CO_2tBu	H	2	*RS*			100.0
3	CH_2CO_2tBu	CO-phenyl	2	*RS*	171–172	$C_{23}H_{26}N_2O_4 \cdot 0.25H_2O$	2.1
4	CH_2CO_2tBu	CO-(4-chlorophenyl)	2	*RS*	169–171	$C_{23}H_{25}N_2O_4Cl$	0.13
5	CH_2CO_2tBu	CO-(3,4-dichlorophenyl)	2	*RS*	183–184	$C_{23}H_{24}N_2O_4Cl_2$	0.028
6	CH_2CO_2tBu	CO-(4-dimethylaminophenyl)	2	*RS*		$C_{25}H_{31}N_3O_4 \cdot 0.75H_2O$	50.00
7	CH_2CO_2tBu	$CO(CH_2)_2$-(3-indolyl)	2	*RS*		$C_{27}H_{31}N_3O_4 \cdot 0.5H_2O$	2.00
8	CH_2CO_2tBu	CO-(2-indolyl)	2	*RS*	121.5–123	$C_{25}H_{27}N_3O_4$	0.007
9	CH_2CO_2tBu	CO-(2-indolyl)	1	*RS*	195–196	$C_{24}H_{25}N_3O_4$	0.20
10	CH_2CO_2tBu	CO-(2-indolyl)	3	*RS*	188–189	$C_{26}H_{29}N_3O_4 \cdot 1H_2O$	0.06
11	CH_2CO_2Et	CO-(2-indolyl)	2	*RS*	238–240	$C_{23}H_{23}N_3O_4$	0.11
12	benzyl	CO-(2-indolyl)	2	*RS*	223–225	$C_{26}H_{23}H_3O_2$	0.035
13	CH_3	CO-(2-naphthyl)	2	*RS*	186.5–188	$C_{22}H_{20}N_2O_2$	6.8
14	CH_2CO_2H	CO-(2-naphthyl)	2	*RS*	235–237	$C_{23}H_{20}N_2O_4 \cdot 1H_2O$	2.3
15	CH_2CO_2tBu	CO-(2-naphthyl)	2	*RS*	162.5–163.5	$C_{27}H_{28}N_2O_4$	0.0075
16	CH_2CO_2tBu	CH_2-(2-naphthyl)	2	*RS*		$C_{27}H_{30}N_2O_3$	0.004
17	CH_2CO_2tBu	$COCH_2$-(2-naphthyl)	2	*RS*	70–72	$C_{28}H_{30}N_2O_4 \cdot 0.25H_2O$	2.7
18	CH_2CO_2tBu	CO-(2-indolyl)	2	*S*	138–140	$C_{25}H_{27}N_3O_4$	0.2
19	CH_2CO_2tBu	CO-(2-indolyl)	2	*R*	122–123.5	$C_{25}H_{27}N_3O_4$	0.003
20	CH_2CO_2tBu	CO-(2-naphthyl)	2	*R*	164–165.5	$C_{27}H_{28}N_2O_4$	0.0042

[a] All compounds analyzed for C, H, and N within ±0.4% (except **2**, where C was 0.44% lower than calcd). [b] IC_{50} (μM) for half-maximal inhibition of binding of ^{125}I-CCK-8 to CCK receptors in rat pancreatic tissue. [c] Reference 5.

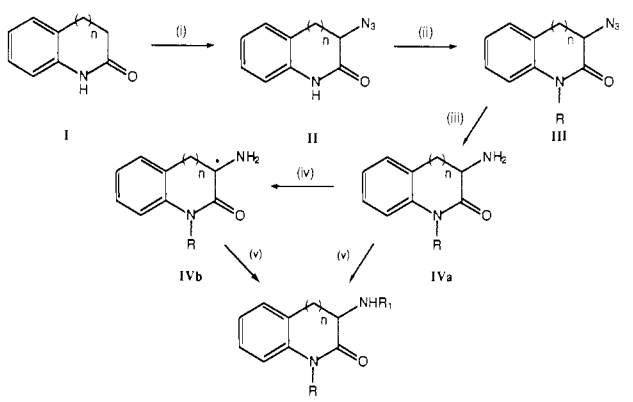
lective, in vivo antagonist of the pancreatic CCK receptor although unfortunately its potency is rather modest (K_i = 0.6 ± 0.2 μm) and asperlicin is not orally active at useful levels. This interesting natural product lead contains a benzodiazepine part-structure, which Evans et al.[6] hypothesized to be the key structural component responsible for its CCK antagonism.[5] Indeed by simplifying the molecule to this core and then exploring substitution patterns in light of some of the essential features of the CCK structure, Evans et al. synthesized L-364,718 (1),[6] which was shown by Chang and Lotti[5] to be a specific antagonist of the pancreatic CCK receptor that is subnanomolar in potency and orally active. This compound is to our knowledge the first potent nonpeptide antagonist to be designed of a neuropeptide.



L-364,718 (1)

We were interested to test compounds structurally related to the benzodiazepine antagonists[6-9] and report here that high levels of CCK inhibition can also be obtained with appropriately substituted benzolactams. Thus, the benzodiazepine part-structure per se is not a prerequisite for CCK antagonism.

Scheme I[a]



[a] (i) References 10 and 11; (ii) RX/NaH/THF; (iii) H_2, Pd/C; (iv) D- or L-tartaric acid; (v) R_1CO_2H, or R_1COCl, or R_1CHO, $NaCNBH_4$.

Chemistry

The benzolactam antagonists reported here were synthesized according to the route outlined in Scheme I. The 3-azidobenzazepinone (n = 2) and 3-azidobenzazocinone (n = 3) intermediates II were prepared via bromination of the parent benzolactams followed by azide displacement and, subsequently, were alkylated with *tert*-butyl iodoacetate, iodomethane, or benzyl bromide with sodium hydride in THF according to methods reported previously by Parsons[10] and Watthey.[11] Likewise, we have reported the conversion of these compounds to 3-aminobenzolactams IVa via hydrogenation with Pd/C (10%) at 40 psi. The 3-aminotetrahydroquinolinone IVa (R = H, n = 1) was synthesized following the route of Davis[12] and alkylated

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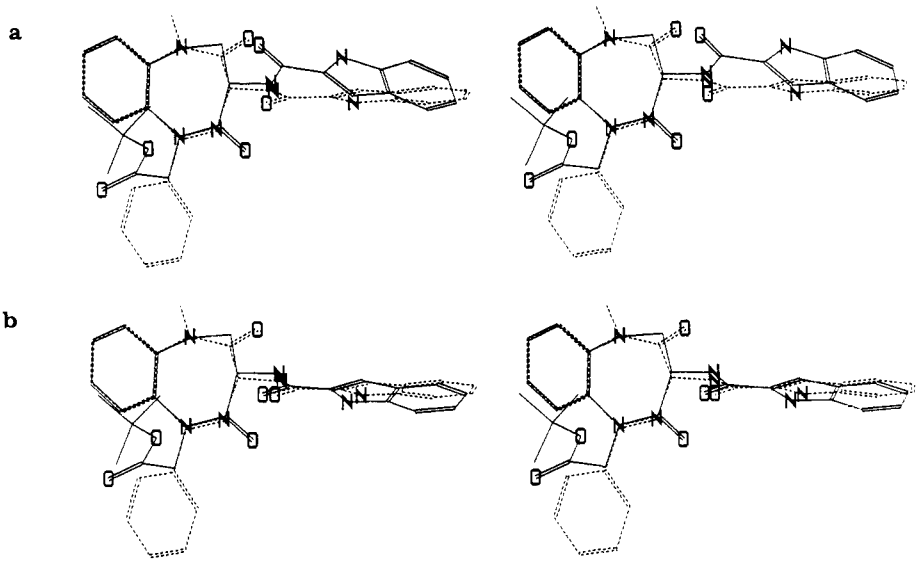

Figure 1. Stereo plots of (a) the superposed minimum-energy-modeled structures of **19** (solid line) and **1** (dashed line) and (b) the same superposition after rotation about the C-3 CH–NH bond of **19**.

with *tert*-butyl iodoacetate under standard conditions. The 3-aminobenzolactam IVa (n = 2) was resolved with D- or L-tartaric acid to give the respective R or S isomers.

3-Aminobenzolactams IV were acylated by peptide coupling techniques. In general, compound IV and the corresponding carboxylic acid were combined with dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole hydrate in CH_2Cl_2 at room temperature and stirred overnight, at which time reaction was usually complete. When indole-2-carboxylic acid was employed, yields were higher and more reproducible if the acid chloride was used. Indole-2-carboxylic acid was combined with excess thionyl chloride in $CHCl_3$ at room temperature. After 6–8 h, the reaction mixture was evaporated, redissolved in $CHCl_3$, and reacted with the appropriate 3-aminobenzolactam and Et_3N to provide amide V.

Compound **15** was prepared by reductive alkylation in a two-step sequence. Amine IV was allowed to stir with an excess of 2-naphthaldehyde in methanol for 1 h followed by addition of $NaCNBH_4$ over 6 h.

All compounds were purified by chromatography on silica gel with mixtures of ethyl acetate and hexane as eluting solvents. Most of the compounds were isolated as crystallizable solids whose melting points are reported in Table I. Compounds **5**, **6**, and **15** were found to be oils or glassy solids.

Results and Discussion

Benzolactams were of interest to us as possible CCK antagonists on the basis of several structural and conformational similarities that they share with benzodiazepines. We had access to a number of *N*-(carboxymethyl)benzolactam derivatives as a result of our earlier work with these compounds as angiotensin converting enzyme inhibitors.[10] This type of substituted benzolactam could be adapted to CCK antagonism by making changes in substituent groups and stereochemistry which are described below.

In Table I we show the structures and the receptor binding data that were obtained with some of the benzolactams prepared in this study. Inhibition of ^{125}I-CCK binding to rat pancreas and guinea pig brain receptors was determined. However, in Table I we show only the pancreas data since in all cases the IC_{50}'s of these compounds were greater than 10 μM on the brain receptor.

Most of our structure–activity studies were done with benzolactams bearing an *N*-[(*tert*-butoxycarbonyl)methyl] substituent at the N-1 position. With that group held constant, it can seen from Table I that increasing lipophilicity of the N-3 acyl group generally enhanced receptor binding. The fact that a 2-indolyl group contributed to high activity is consistent with studies leading to the design of L-364,718,[6] and in detail, the considerable difference between the contribution of this group and a 4-chlorobenzoyl group (compounds 4 and 8) is reflected in SAR studies of the triazolo[4,3-*a*]benzodiazepine CCK antagonists.[8] Also of interest in the 3-position is the excellent activity which is retained when the carboxamide group is replaced by an $-NHCH_2-$ functionality (compound **16**). Apparently, an amide carbonyl oxygen in this position is not involved in direct interaction with the receptor.

The stereochemistry at C-3 has a pronounced effect on activity, with the R isomer **19** being nearly a 100-fold more active than the S isomer **18**. An R absolute configuration is opposite to that determined for highly active benzodiazepines such as L-364,718 (**1**). In order to examine this stereochemical preference, we modeled the three-dimensional structures of **1** and **19**. In each case, the seven-membered ring adopted a pseudoboat conformation, with the C-3 substituent occupying a pseudoequatorial position. Superposition of these two structures, while maintaining overlap of the benzodiazepine and benzolactam core structures, led to the match shown in Figure 1a. From this superposition, we are led to propose that the *N*-[(*tert*-butoxycarbonyl)methyl] group of compound **19** may share some of the same space on the receptor as the 4-phenyl group of compound **1**. The poor activities of a methyl analogue, **13**, and a carboxymethyl analogue, **14**, are consistent with this hypothesis. In order to superimpose the indolyl groups as shown in Figure 1b, rotation was required around the C-3 CH–NH bond of compound **19**, at a calculated cost of approximately 1.5 kcal/mol. This energy difference may contribute to the decreased activity of **19** relative to **1**.

Lactam ring size is also important for activity. With R_1 in all cases a 2-indolyl group, increasing potency can be seen in benzolactams of ring sizes 6 < 8 < 7 (compounds

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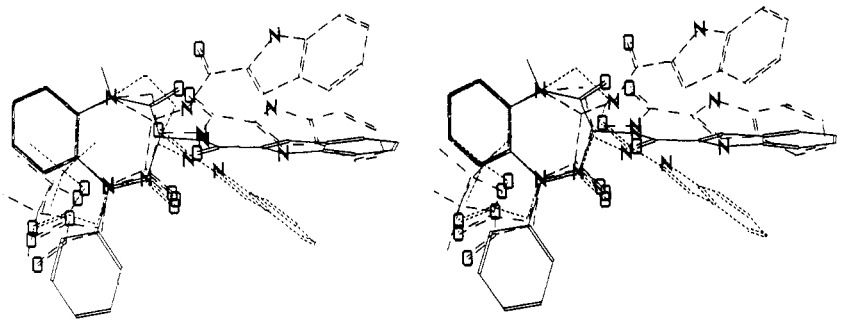

Figure 2. Superposition of the modeled structures of 1 (solid line), 19 (long-dash line), (*S*)-9 (medium-dash line), and (*S*)-10 (short-dash line).

9, 10, and 8). In order to explore this observation, we compared minimum-energy models of 1, 19, (*S*)-9, and (*S*)-10; the superposition of these models is shown in Figure 2. The poor alignment of the indolyl groups of 9 and 10 with that of 1 is in accord with the reduced activity of these benzolactams.

In addition, we note that the potent benzolactam CCK antagonists described in this study can be predicted to have negligible angiotensin converting enzyme (ACE) inhibitory activity. The substituents at C-3 in lactam ACE inhibitors include Zn^{2+} binding functionality which is absent in the current series, and furthermore such substituents are preferred in the *S* not *R* configuration as was found in the CCK antagonists described above.[14]

Several of the more active benzolactam CCK antagonists were tested for in vivo activity by using a CCK-8-induced inhibition of gastric emptying protocol described earlier.[15] Compound 8, the racemic analogue of our most active compound 19, antagonized the inhibition of gastric emptying produced by CCK with an ED_{50} of 2.6 mg/kg po, which was slightly better than the naphthyl analogue 20 (ED_{50} = 6.8 mg/kg po). For comparison, L-364,718 (1) is active in this protocol with an ED_{50} of 0.04 mg/kg po.[15]

In summary, we have demonstrated that nanomolar antagonists of the pancreatic CCK receptor can be synthesized by using benzolactam chemistry. The best of these compounds are orally active although their potencies are less than comparably 3-substituted benzodiazepines. Molecular modeling studies suggest that the benzodiazepine and benzolactam core conformations, the 3-substituents, and a hydrophobic substituent at N-1 of the benzolactams or at C-5 of the benzodiazepines can be similarly oriented in space and may interact with similar binding areas on the CCK receptor.

Experimental Section

Molecular Modeling. All modeled geometries were sketched, normalized, and optimized by using the Merck molecular modeling system MOLEDIT,[16] which includes a modified MM2 force field.[17] All molecular superpositions were performed by using the COMPARE facility within MOLEDIT.

Biological Evaluation. ^{125}I-CCK binding assays in rat pancreas and guinea pig brain were as described previously.[5] CCK antagonist activity in vivo was determined by using CCK-8 inhibition of charcoal meal as reported earlier.[15]

Chemistry. General Methods. ^{1}H NMR spectra were recorded on a Varian XL300 pulsed Fourier transform instrument or a Varian T-60. Mass spectra were recorded on a Finnigan MAT731 mass spectrometer.

Elemental analyses were within ±0.4% of the theoretical values. Thin-layer chromatography was carried out on silica gel MK6L (Whatman, 0.2-mm) glass-backed plates. Preparative medium-pressure chromatography (MPLC) was carried out with Lobar LiChroprep Si60 (E. Merck, 40–63-mm) prepacked columns.

3-Amino-1,2,3,4-tetrahydroquinolin-2-one was prepared according to the method of Davis.[12] 3-Azido-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one, 3-amino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one, 3-amino-1-(carbo-*tert*-butoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one, 3(*R*)- and 3(*S*)-amino-1-(carbo-*tert*-butoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one, and 3-amino-1-(carbo-*tert*-butoxymethyl)-3,4,5,6-tetrahydro-1*H*-1-benzazocin-2-one were prepared according to the procedures of Watthey[11] and Parsons.[10]

Method A. 3-(Benzoylamino)-1-(carbo-*tert*-butoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (3). To a solution of 3-amino-1-(carbo-*tert*-butoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (0.4 g, 0.00144 mol), benzoic acid (0.185 g, 0.0015 mol), and 1-hydroxybenzotriazole hydrate (0.205 g, 0.0015 mol) in 10 mL of CH_2Cl_2 was added 1,3-dicyclohexylcarbodiimide (0.313 g, 0.00151 mol). This reaction mixture was stirred 12 h at room temperature. The reaction was filtered and washed successively with 5% Na_2CO_3, 5% citric acid, and a saturated solution of $NaHCO_3$. The organic fraction was then filtered through a thin pad of $MgSO_4$ and evaporated in vacuo. The product was chromatographed on silica gel (MPLC), eluting with hexanes/EtOAc (7:3) to give the title compound (0.59 g) as a white crystalline solid: TLC (silica, hexanes/EtOAc, 7:3) R_f = 0.3; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.0–2.15 (dq, 1 H), 2.6–2.7 (dd, 1 H), 2.8–2.95 (m, 1 H) 3.35–3.5 (dq, 1 H), 4.4 (q, 2 H), 4.6–4.8 (m, 1 H), 7.1 (d, 1 H), 7.15–7.35 (m, 4 H), 7.35–7.5 (m, 3 H), 7.8, (d, 2 H); MS, *m/e* 394 (M^+); mp 171–173 °C.

In like manner as the above sequence with the appropriate amine and carboxylic acid, compounds 4–7, 15, and 17 were prepared.

Method B. 1-(Carbo-*tert*-butoxymethyl)-3-[(2-indolylcarbonyl)amino]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (8). To a solution of indole-2-carboxylic acid (0.165 g, 0.001 mol) in 3 mL of $CHCl_3$ at room temperature was added thionyl chloride (0.25 mL, 0.0034 mol). After stirring for 8 h, the reaction mixture was evaporated in vacuo. To the acid chloride in 3 mL of $CHCl_3$ was added 3-amino-1-(carbo-*tert*-butoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepinone (0.3 g, 0.001 mol) and Et_3N (0.14 mL, 0.001 mol), and the reaction mixture was stirred at room temperature. After 3 h the reaction mixture was partitioned between H_2O and EtOAc. The H_2O layer was extracted with EtOAc, and the combined organic fractions were dried over Na_2SO_4, filtered through a thin pad of $MgSO_4$, and evaporated in vacuo. The crude product was chromatographed on silica gel (MPLC), eluting with EtOAc/hexanes (1:2) to afford the title compound 8 (0.3 g, 70%) as a white solid: TLC (silica, EtOAc/hexanes, 1:2) R_f = 0.77; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9 H), 2.05–2.15 (dq, 1 H), 2.6–2.7 (dd, 1 H), 2.75–2.95 (m, 1 H), 4.5 (q, 2 H), 4.7–4.8 (m, 1 H), 6.95 (s, 1

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H), 7.1–7.2 (m, 2 H), 7.2–7.4 (m, 6 H), 7.65 (d, 1 H), 9.5 (s, 1 H); MS, m/e 433 (M^+); mp 121.5–123 °C.

In like manner as the above sequence with the appropriate amine and carboxylic acid, compounds **9**, **10**, and **12** were prepared.

1-(Carbethoxymethyl)-3-[(2-indolylcarbonyl)amino]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11). A solution of 3-amino-1-(carbo-*tert*-butoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (1.2 g) in 30 mL of EtOH was cooled to 0 °C and saturated with HCl gas. The solution was sealed and stirred for 12 h at room temperature, whereupon it was concentrated in vacuo. The residue was dissolved in EtOAc, washed with a 10% solution of K_2CO_3, filtered through a pad of $MgSO_4$, and concentrated to give 0.95 g of 3-amino-1-(carbethoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. The title compound **11** (0.133 g, 19%) was prepared from the aformentioned ethyl ester (0.4 g, 0.0015 mol) according to the procedures in method B: TLC (silica, EtOAc/hexanes, 1:1) R_f = 0.65; ^{1}H NMR ($CDCl_3$) δ 1.2–1.35 (t, 3 H), 2.0–2.15 (m, 1 H), 2.6–2.75 (m, 1 H), 2.8–2.95 (m, 1 H), 3.35–3.5 (m, 1 H), 4.1–4.3 (m, 3 H), 4.4–4.8 (ABq, 2 H), 6.9 (s, 1 H), 7.1–7.4 (m, 8 H), 7.6 (d, 1 H), 9.4 (br s, 1 H) MS (FAB), m/e 406 (M + 1); mp 238–240 °C.

3-[(2-Naphthylcarbonyl)amino]-1-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (13). To a suspension of NaH (0.126 g, 50% in oil, 0.0026 mol, washed three times with hexanes) in 2.5 mL of THF at 0 °C was added dropwise a solution of 3-azido-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (0.5 g, 0.0025 mol) and iodomethane (0.37 mL, 0.0052 mol) in 3 mL of THF. After stirring for 30 min, the reaction was quenched with a saturated solution of NH_4Cl and extracted twice with EtOAc (10 mL). The combined organic fractions were filtered through a pad of $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (MPLC), eluting with hexanes/EtOAc (7:3) to give 0.31 g of 3-azido-1-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. This material was dissolved in 6 mL of EtOH with Pd/C (10%, .06 g) and hydrogenated at 40 psi for 18 h. The reaction mixture was filtered and evaporated in vacuo to provide 0.275 g of 3-amino-1-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one: ^{1}H NMR (CD_3OD) δ 1.8–3.0 (m, 4 H), 3.4 (s, 3 H), 3.4–3.8 (m, 1 H), 7.2 (m, 4 H). Title compound **13** (0.29 g, 60%) was prepared from 3-amino-1-methyl-2,3,4,5-1*H*-1-benzazepin-2-one (0.27 g, 0.0014 mol) and 2-naphthoic acid (0.254 g, 0.0014 mol) according to method A: TLC (silica, EtOAc/hexanes, 1:1) R_f = 0.48; ^{1}H NMR ($CDCl_3$) δ 2.0–2.15 (m, 1 H), 2.6–2.75 (m, 1 H), 2.8–3.0 (m, 2 H), 3.5 (s, 3 H), 4.65–4.75 (m, 1 H), 7.15–7.4 (m, 4 H), 7.4–7.6 (m, 3 H), 7.8–8.0 (m, 4 H), 8.3 (s, 1 H); MS, m/e 344 (M^+); mp 186.5–188 °C.

1-(Carbomethoxy)-3-[(2-naphthylcarbonyl)amino]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14). A solution of 1-(carbo-*tert*-butoxymethyl)-3-[(2-naphthylcarbonyl)amino]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**15**) (0.04 g) in 1 mL of CH_2Cl_2 and 1 mL of trifluoroacetic acid was stirred for 3 h at room temperature and then thoroughly evaporated in vacuo: ^{1}H NMR (CD_3OD) δ 2.3–2.45 (m, 1 H), 2.45–2.6 (m, 1 H), 2.65–2.7 (m, 1 H), 3.4–3.6 (m, 1 H), 4.6 (q, 2 H), 4.65–4.75 (m, 1 H), 7.2–7.45 (m, 4 H), 7.5–7.65 (m, 2 H), 7.8–8.0 (m, 4 H), 8.4 (s, 1 H), 8.65 (d, 1 H); MS (FAB), m/e 389 (M + 1); mp 235–237 °C.

1-(Carbo-*tert*-butoxymethyl)-3-[(2-naphthylmethyl)amino]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (16). A solution of 3-amino-1-(carbo-*tert*-butoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (0.3 g, 0.001 mol), 2-naphthaldehyde (0.48 g, 0.003 mol), and acetic acid (0.12 mL) in 6 mL of MeOH was stirred 1 h at room temperature. To this solution was added dropwise a solution of $NaCNBH_3$ (0.19 g, 0.003 mol) in 6 mL of MeOH over a 6-h period. After stirring for an additional 8 h, the reaction mixture was evaporated in vacuo and partitioned between H_2O and EtOAc. The organic fraction was filtered through a pad of $MgSO_4$, concentrated under vacuum, and purified (MPLC), eluting with EtOAc to afford the title compound **16** (0.13 g, 32%) as an oil: TLC (silica, EtOAc) R_f = 0.48; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9 H), 1.9–2.1 (m, 1 H), 2.35–2.45 (m, 1 H), 2.5–2.65 (m, 1 H), 3.15–3.3 (m, 1 H), 3.3–3.4 (m, 1 H), 3.55–4.0 (q, 2 H), 4.4–4.6 (q, 2 H), 6.5 (d, 1 H), 7.05 (d, 1 H), 7.1–7.8 (m, 11 H); MS (FAB), m/e 431 (M + 1).

1-(Carbo-*tert*-butoxymethyl)-3(*S*)-[(2-indolylcarbonyl)amino]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (18). The title compound **18** (0.24 g, 80%) was prepared from 3(*S*)-amino-1-(carbo-*tert*-butoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (0.2 g, 0.0007 mol) and indole-2-carboxylic acid (0.11 g, 0.0007 mol) by method B: TLC (silica, hexanes/EtOAc, 2:1) R_f = 0.4; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9 H), 2.05–2.2 (dq, 1 H), 2.6–2.75 (dd, 1 H), 2.8–2.95 (m, 1 H), 3.35–3.5 (dq, 1 H), 4.5 (q, 2 H), 4.7–4.8 (m, 1 H), 6.95 (s, 1 H), 7.1–7.2 (m, 2 H), 7.2–7.35 (m, 6 H), 7.4 (d, 1 H), 9.5 (s, 1 H); MS, m/e 433 (M^+); mp 138–140 °C; $[\alpha]^{20}_D$ = −123.3° (*c* 1.02, EtOH).

1-(Carbo-*tert*-butoxymethyl)-3(*R*)-[(2-indolylcarbonyl)amino]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (19). The title compound **19** (0.2 g, 56%) was prepared from 3(*R*)-amino-1-(carbo-*tert*-butoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (0.24 g silica, hexanes/EtOAc, 2:1) R_f = 0.4; ^{1}H NMR ($CDCl_3$), same as for compound **18**; MS, m/e 433 (M^+); mp 122–123.5 °C; $[\alpha]^{20}_D$ = +141.33° (*c* 0.64, EtOH).

1-(Carbo-*tert*-butoxymethyl)-3(*R*)-[(2-naphthylcarbonyl)amino]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (20). The title compound (0.70 g, 46%) was prepared from 3-(*R*)-amino-1-(carbo-*tert*-butoxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (0.1 g, 0.00034 mol) and 2-naphthoic acid (0.05 g, 0.00034 mol) according to method A. TLC (silica, hexanes/EtOAc, 1:1) R_f = 0.48; ^{1}H NMR ($CDCl_3$) and MS, same as for compound **15**; mp 164–165.5 °C; $[\alpha]^{20}_D$ = +116.78° (*c*, 0.288 MeOH).