

evaporated. The residue was partitioned between EtOAc and water, and the organic layer was washed with water, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was purified by chromatography on  $\text{SiO}_2$  using  $\text{CH}_2\text{Cl}_2$  plus 0-5% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from  $\text{Et}_2\text{O}$  to give title compound 29: yield 0.17 g (41%); mp 87-88 °C. Anal. ( $\text{C}_{25}\text{H}_{34}\text{ClN}_3\text{O}_7$ ) C, H, N.

**N-(2-Aminoethyl)-2-[[2-[[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]acetamide (30).** A solution of 24 (0.58 g, 1.2 mmol) and 1,2-diaminoethane (5 mL) in MeOH (10 mL) was stirred at room temperature for 18 h and evaporated. The residue was partitioned between EtOAc and water, and the organic layer was washed with water, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was purified by chromatography on  $\text{SiO}_2$  using  $\text{CH}_2\text{Cl}_2$  plus 10-30% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from EtOAc to give title compound 30: yield 0.16 g (40%); mp 93-99 °C. Anal. ( $\text{C}_{24}\text{H}_{33}\text{ClN}_4\text{O}_6$ )C: calcd, 56.63; found, 56.00; H, N.

**Ethyl 2-[[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]propionate (31).** A mixture of 1 (4.08 g, 10 mmol), ethyl 2-bromopropionate (2.00 g, 11 mmol), and  $\text{K}_2\text{CO}_3$  (2.8 g, 20 mmol) in acetonitrile (120 mL) was heated under reflux for 24 h, filtered, and evaporated. The residue was partitioned between EtOAc and water, and the organic layer washed with water, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was purified by chromatography on  $\text{SiO}_2$  using  $\text{CH}_2\text{Cl}_2$  plus 0-2% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from  $\text{Et}_2\text{O}$  to give title compound 31: yield 1.40 g (28%); mp 89-90 °C. Anal. ( $\text{C}_{25}\text{H}_{33}\text{ClN}_2\text{O}_7$ ) C, H, N.

**2-[[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]propionamide (32).** A solution of 31 (1.02 g, 2.0 mmol) and concentrated aqueous ammonia (25 mL) in EtOH (30 mL) was stirred at room temperature for 14 days and evaporated. The residue was partitioned between EtOAc and water, and the organic layer was washed with water, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was purified by chromatography on  $\text{SiO}_2$

using  $\text{CH}_2\text{Cl}_2$  plus 0-5% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from EtOAc to give title compound 32: yield 0.56 g (59%); mp 124-126 °C. Anal. ( $\text{C}_{23}\text{H}_{30}\text{ClN}_3\text{O}_6$ ) C, H, N.

**2-[[2-[[4-(2-Chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyrid-2-yl]methoxy]ethyl]amino]-2-methylpropionamide (33).** A mixture of 1 (4.08 g, 10 mmol), 2-bromo-2-methylpropionamide (1.66 g, 10 mmol), and  $\text{K}_2\text{CO}_3$  (2.07 g, 15 mmol) in  $\text{CH}_3\text{CN}$  (50 mL) was heated under reflux for 18 h, filtered, and evaporated. The residue was partitioned between EtOAc and water, and the organic layer was washed with water, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was purified by chromatography on  $\text{SiO}_2$  using  $\text{CH}_2\text{Cl}_2$  plus 0-5% MeOH as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from MeOH to give title compound 33: yield 0.45 g (9%); mp 79-81 °C. Anal. ( $\text{C}_{24}\text{H}_{32}\text{ClN}_3\text{O}_6\cdot\text{H}_2\text{O}$ )C: calcd, 56.30; found, 56.89; H, N.

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**Registry No.** 1, 88150-42-9; 4, 123700-09-4; 5, 123700-10-7; 6, 123700-11-8; 7, 123700-12-9; 8, 103069-16-5; 9, 123700-13-0; 10, 123700-14-1; 11, 123700-15-2; 12, 123700-16-3; 13, 123700-17-4; 13-maleate, 123700-18-5; 14, 123700-19-6; 15, 123700-20-9; 16, 123700-21-0; 17, 123700-22-1; 18, 123700-23-2; 19, 123700-24-3; 20, 123700-25-4; 21, 123700-26-5; 22, 123700-27-6; 23, 123700-28-7; 24, 123700-29-8; 25, 123700-30-1; 26, 123700-31-2; 27, 123700-32-3; 28, 123700-33-4; 29, 123700-34-5; 30, 123700-35-6; 31, 123700-36-7; 32, 123700-37-8; 33, 123700-38-9;  $\text{EtO}_2\text{CCH}_2\text{NCO}$ , 2949-22-6;  $\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$ , 107-15-3;  $\text{H}_2\text{NCH}_2\text{CONH}_2$ , 598-41-4;  $\text{NH}_2\text{S-O}_2\text{NH}_2$ , 7803-58-9;  $\text{MeOCH}_2\text{CH}_2\text{NH}_2$ , 109-85-3;  $\text{H}_3\text{CCH}(\text{Br})\text{CO}_2\text{Et}$ , 41978-69-2; nicotinic acid, 59-67-6; 2-pyrazinecarboxylic acid, 98-97-5; 6-hydroxypyrazine-3-carboxylic acid, 5006-66-6; 4-amino-2-hydroxypyrimidine, 71-30-7; 1-(2-aminoethyl)-imidazolidin-2-one, 6281-42-1; 2-bromo-2-methylpropionamide, 7462-74-0.

## Novel Glutamic Acid Derived Cholecystokinin Receptor Ligands

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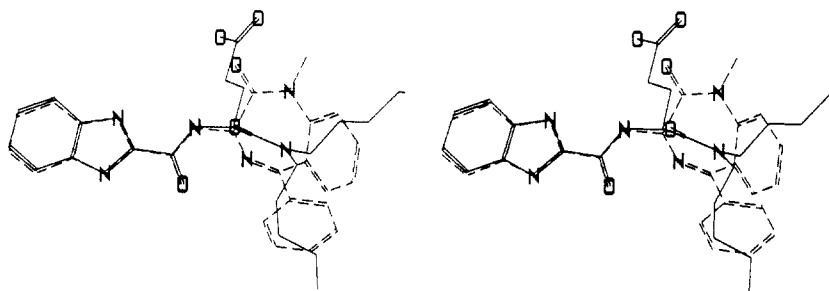
Novel aryl amide analogues of glutamic acid dialkylamide have been synthesized to test for a possible structural analogy between glutamic acid and benzodiazepine CCK antagonists such as compounds 2 and 24 (lorglumide and MK-329, respectively). In support of the structural model, certain of these hybrid compounds are more potent in pancreas CCK radioligand binding assays than corresponding lorglumide-type reference compounds. Modifications previously found in the benzodiazepine antagonists to result in brain CCK/gastrin receptor selectivity were also incorporated to produce an aryl urea series of glutamic acid analogues. None of these compounds were brain CCK/gastrin selective; however, one was potent and selective in the pancreas binding assay. The model appears to be most useful in the design of selective ligands for the pancreas type CCK receptor.

Cholecystokinin (CCK) was originally discovered as a gastrointestinal peptide,<sup>1</sup> and more recently it has been implicated as a neurotransmitter or neuromodulator.<sup>2</sup> The effects of CCK on pancreatic secretions, gut motility, and satiety have been studied intensively.<sup>3,4</sup> These and other actions are mediated by at least two CCK receptor subtypes termed CCK-A and CCK-B.<sup>5</sup> The former receptor

is found primarily in tissue types such as pancreas, gall bladder, and colon, although isolated regions have been localized in the central nervous system (CNS).<sup>5,6</sup> The CCK-A receptors in the pancreas have been shown to be linked to phosphatidylinositol turnover.<sup>7</sup> The primary CCK receptor subtype in the CNS is CCK-B,<sup>8</sup> which has

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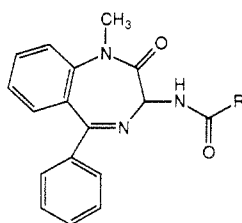
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**Figure 1.** Computer superposition of the X-ray structure of **24** and a low-energy conformation of **6**.

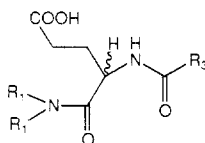
similar ligand specificities to the gastrin receptor found in the stomach.<sup>9-11</sup> Recent evidence is consistent with coupling of a population of CCK-B receptors to nucleotide regulatory proteins, although a specific second messenger system is not yet established.<sup>12</sup>

Investigations of the role of CCK in normal physiology and disease states have been facilitated by the recent development of potent, orally active nonpeptide antagonists of CCK. A 3-[(2-indolylcarbonyl)amino]-1,4-benzodiazepine **24** (MK-329, formerly L-364,718) from Merck



MK-329, **24**, R = 2-Indolyl, Stereo = S  
L-365,260, **25**, R = m-Me-Phenylamino, Stereo = R

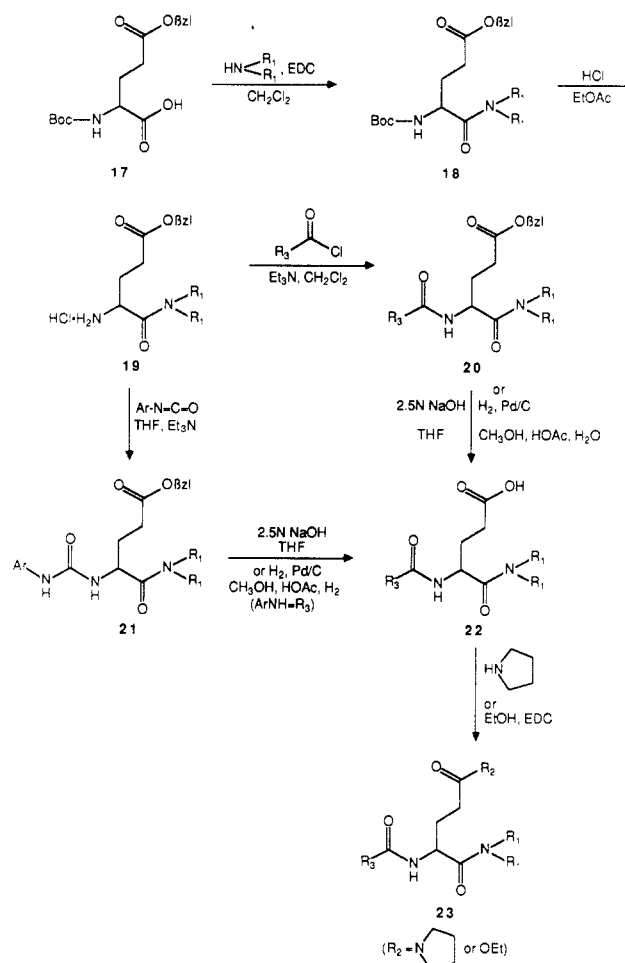
is the most potent known CCK-A selective antagonist with receptor affinity comparable to that of the native peptide.<sup>13-15</sup> This compound is over 1000-fold less potent at the CCK-B type receptor. Compound **2** (lorglumide,



Proglumide **1**, R<sub>3</sub> = Ph, R<sub>1</sub> = n-Pr  
Lorglumide **2**, R<sub>3</sub> = 3,4-di-Cl-Ph, R<sub>1</sub> = n-Pentyl

Rotta)<sup>16</sup> is a derivative of DL-glutamic acid, and it also

#### Scheme I. Methods of Synthesis of Compounds of Table I



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exhibits good CCK-A selectivity although potency is significantly lower than that for **24**. Compound **2** was developed from the weak, nonselective CCK/gastrin antagonist **1** (proglumide).<sup>17</sup> Very recently, a second 3-substituted benzodiazepine-type antagonist from Merck (**25**, L-365,260) with high potency and selectivity for the CCK-B and gastrin receptor types has been introduced.<sup>10,11</sup>

As part of our investigations of CCK antagonists of various structural types, it was of interest to determine if a relationship could be established between structural features of the benzodiazepine-type antagonists and the glutamic acid derivatives. Our initial working hypothesis was that the indolecarboxamide and 3,4-dichlorobenzamide groups of **24** and **2**, respectively, bind to the same receptor site. Furthermore, the two benzene rings of the former

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Table I. Receptor Binding Data for Glutamic Acid Analogues

no.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	stereo.	IC <sub>50</sub> , μM		
					[ <sup>125</sup> I] CCK		[ <sup>125</sup> I] gastrin:
					pancreas	brain	gastric glands
1	<i>n</i> -Pr	OH	Ph	<i>RS</i>	250	800	900
2	<i>n</i> -Pentyl	OH	3,4-Cl <sub>2</sub> -Ph	<i>RS</i>	0.018	2.2	1.9
3	<i>n</i> -Pr	OH	2-indolyl	<i>S</i>	3.7	88	17
4	<i>n</i> -Pr	OH	2-indolyl	<i>R</i>	1.1	27	39
5	<i>n</i> -Pr	OCH <sub>2</sub> Ph	2-indolyl	<i>R</i>	0.81	4.6	7.0
6	<i>n</i> -Pentyl	OH	2-indolyl	<i>R</i>	0.0076	0.23	0.17
7	cyclohexyl	OH	2-indolyl	<i>R</i>	0.059	3.4	4.1
8	cyclohexyl	OCH <sub>2</sub> Ph	2-indolyl	<i>R</i>	0.2	30	100
9	<i>n</i> -Pentyl	OH	<i>p</i> -Cl-Ph-NH	<i>RS</i>	0.14	0.63	0.7
10	<i>n</i> -Pentyl	OCH <sub>2</sub> Ph	<i>p</i> -Cl-Ph-NH	<i>RS</i>	9.3	16	44
11	<i>n</i> -Pentyl	OE <sub>t</sub>	<i>p</i> -Cl-Ph-NH	<i>RS</i>	1.2	1	4.5
12	<i>n</i> -Pentyl	pyrrolidinyl	<i>p</i> -Cl-Ph-NH	<i>RS</i>	0.68	0.25	0.43
13	<i>n</i> -Pentyl	OH	<i>m</i> -OMe-Ph-NH	<i>S</i>	0.54	9.7	13
14	<i>n</i> -Pentyl	OH	<i>m</i> -OMe-Ph-NH	<i>R</i>	0.0045	0.71	0.31
15	<i>n</i> -Pentyl	pyrrolidinyl	<i>m</i> -OMe-Ph-NH	<i>S</i>	0.17	0.48	0.86
16	<i>n</i> -Pentyl	pyrrolidinyl	<i>m</i> -OMe-Ph-NH	<i>R</i>	0.12	0.063	0.19
24					0.00008	0.27	0.17
25					0.28	0.002	0.0011

antagonist and the two *n*-pentyl chains of the latter correspond in the model. As an experimental test of this hypothesis, a series of glutamic acid analogues which are hybrids of 24 and 1 or 2 were synthesized and tested in three radioreceptor assays. On the basis of structure-activity relationships in the benzodiazepine series,<sup>15</sup> it was anticipated that substitution of indol-2-ylcarbonyl for the benzoyl substituents in the glutamic acid series would produce more potent analogues. Molecular modeling comparisons such as 24 matched with the indol-2-ylcarbonyl analogue of 2 (6, Figure 1) support the plausibility of the proposed structural analogies. In addition, a similar group of analogues incorporating features which led to the reversal of receptor subtype specificity found with 25 was prepared. A preliminary account of part of this work has been reported,<sup>18</sup> and this paper provides additional results and full experimental details. A related study was recently reported by the Abbott group.<sup>19</sup>

**Chemistry.** Scheme I summarizes the syntheses of the analogues contained in Table I. The starting material was either *N*<sup>α</sup>-(*tert*-butoxycarbonyl(Boc))-ε-benzyl-L, D- or -DL-glutamic acid (17). Coupling with the appropriate dialkylamine using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) in methylene chloride provided amides 18 in good yields. The Boc protecting group was then efficiently removed with HCl in ethyl acetate. The resultant amines 19 were then converted to a series of amides (3–8) and a series of ureas (9–16). Side chain protected amides 20 (represented by 5 and 8 in Table I) were obtained by treatment of 19 with aryl acid chlorides in the presence of triethylamine. Treatment of amines 19 with aryl isocyanates and triethylamine produced the side

chain protected ureas 21 (represented by 10 in Table I). Free carboxylic acid derivatives 22 in either the amide (Table I, 3, 4, 6, and 7) or the urea (Table I, 9, 13, and 14) series were obtained by hydrogenolysis or saponification. In certain cases, these acids were then converted to the pyrrolidine amide (Table I, 12, 15, and 16) or ethyl ester (Table I, 11) analogues 23.

These methods of synthesis differ from those reported for 2 and related structures,<sup>17</sup> but they have the distinct advantage of allowing the preparation of the analogues as either enantiomer or in racemic form as desired.

**Biology.** The methods employed for determination of [<sup>125</sup>I]CCK-33 binding to rat pancreas and guinea pig cortex and [<sup>125</sup>I]gastrin binding to guinea pig gastric glands were as described previously.<sup>14</sup> Values shown are the means of triplicate determinations.

**Molecular Modeling.** Two hundred conformations of 6 were generated with a distance geometry algorithm<sup>20</sup> which was incorporated into the Merck molecular modeling system MOLEDT.<sup>21</sup> All amide bonds were restricted to 180° ± 20° and aromatic rings were defined as rigid groups. One hundred forty-one conformers of 6 met the distance criteria. These were minimized within MOLEDT using a modified MM2 force field.<sup>22</sup> A dielectric constant of 50 was employed in order to preclude intramolecular hydrogen bonding. All conformers within 5 kcal/mol of the minimum energy conformer were rigidly superposed on the

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X-ray structure of **24**. These were examined visually for overlap of key structural features.

## Discussion

The results presented in Table I support the proposed structural correspondence between **24** and **1** or **2**. Initially, glutamic acid analogues **3** and **4** in which the benzoyl group of **1** is replaced by indol-3-ylcarbonyl were synthesized. Both of these analogues are about 100-fold more potent than **1** and considerably more CCK-A selective. Surprisingly, there is little difference in receptor binding affinity between these two enantiomers. In contrast, the enantiomer of **2** derived from D-glutamic acid showed a 50-fold greater affinity for pancreatic acini receptors than the L-enantiomer.<sup>16</sup> The result with **3** and **4** suggests that the glutamic acid side chain is not an important receptor-binding element in analogues related to **1**. Consistent with this proposal is the observation that benzyl ester **5** has essentially the same affinity for the CCK-A receptor as **4**. The increased CCK-B and gastrin binding affinities for **5** suggest that this side chain may be more important for interacting with these receptor subtypes.

The analogy to **2** was next pursued by substituting the di-*n*-pentylamide group into **4** to give **6**. This modification resulted in substantial potency increases in the Rotta compounds.<sup>15</sup> In accord with those results, **6** was 100 times more potent than **4**. Compound **6** has 2–3 times better affinity for the CCK-A receptor than **2**, although **2** is slightly more selective versus CCK-B and gastrin receptors. The Abbott study also produced **6** and a slightly more potent hybrid of **24** and **2** (A-65,186) in which the indole of **6** is replaced by a 3-substituted quinoline.<sup>19</sup>

To test whether bis cyclic alkyl amides might be better mimics of the benzodiazepine benzene rings and might even more closely approach the potency of **24** in the glutamic acid analogue series, dicyclohexylamide analogues **7** and **8** were prepared. However, Compound **7** is about 10-fold less potent than **6**.

Compounds **9–16** illustrate attempts to design glutamic acid analogues with increased CCK-B/gastrin receptor selectivity. In the 3-substituted benzodiazepine CCK antagonists, modification of the N<sup>1</sup>-substituent, changing the 3-position amide to a urea, and inverting the 3-position stereochemistry of compounds in the class of **24** were important factors in converting from CCK-A to CCK-B/gastrin receptor selectivity (e.g. **25**).<sup>10</sup> In a group of racemic urea-containing compounds **9–12**, receptor subtype specificity was largely lost as was also seen for certain benzodiazepine urea analogues. Large N<sup>1</sup>-substituents were important in the latter series for obtaining good CCK-B/gastrin selectivity; however, a way to mimic these groups in the glutamic acid series was not found. Side chain ethyl ester or pyrrolidine amide, for example, did not lead to large potency increases at CCK-B/gastrin receptors.

Based on results with **25** and its enantiomer,<sup>10</sup> resolution of glutamic acid ureas might be expected to produce enantiomers with opposite CCK receptor subtype preferences. Comparing **13** and **14** or **15** and **16**, however, shows further that these compounds do not follow the structure-activity pattern of the benzodiazepine ureas. In the case of the *m*-methoxyphenylureas **13** and **14**, both enantiomers are CCK-A selective, and **14** is actually the most potent and selective receptor ligand in either the amide or urea series. Contrasting **13** and **14** with **3** and **4**, the more tightly binding ligands show greater receptor stereospecificity, indicating that the glutamic acid side chain now plays a more significant role. In support of this possibility, conversion of **13** and **14** to side chain pyrrolidine amides **15** and **16** leads to loss of selectivity primarily

due to increased CCK-B/gastrin receptor affinity. Compound **16** is the most potent CCK-B/gastrin receptor ligand in this series. While the structural correspondence for binding to CCK and gastrin receptors between **25** and the glutamic acid ureas appears to be poor, the results suggest that further structure-activity studies based on **10–12** and **16** could produce CCK-B/gastrin selective analogues in this series.

## Conclusion

The results of this paper show that a model in which CCK receptor binding elements of benzodiazepine **24** and glutamic acid analogues **1** and **2** are matched has proven useful in designing glutamic acid based CCK-A selective receptor ligands of increased potency. Extension of this structural analogy to the CCK-B/gastrin selective antagonist **25**, however, did not lead to glutamic acid derivatives with analogous selectivity. The model appears to be most useful for design of novel CCK-A selective receptor ligands.

## Experimental Section

Melting points (Thomas-Hoover melting point apparatus) are uncorrected. Spectra were obtained as follows: EI mass spectra on a VG MM 7035 mass spectrometer; FAB mass spectra on a VG MM/ZAB-HF spectrometer, <sup>1</sup>H NMR spectra on a Varian EM-390 or Nicolet NT-360 spectrometer, with Me<sub>4</sub>Si as internal standard. HPLC was carried out on a Hewlett-Packard Model 1084B liquid chromatograph using a Waters C-18 column. Elemental analyses for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of the theory unless noted otherwise.

Analytical TLC was carried out on 250-μm, 5 × 20 cm silica gel plates (E. Merck) using ultraviolet light/phosphomolybdic acid for visualization.

**Syntheses.** Specific examples presented below illustrate general synthetic methods outlined in Scheme I. Other physical data are given in Table II. In general, samples prepared for physical and biological studies were dried in high vacuum (5 μm) over P<sub>2</sub>O<sub>5</sub> for 18 h at temperatures ranging from ambient to 110 °C, depending on the sample melting point. Despite these measures, some of the compounds remained solvated (Table II). Where analytical data have been presented for such solvates, the presence of all indicated solvents has been verified by NMR.

**N<sup>α</sup>-Boc-ε-benzyl-D-glutamic Acid Dipropylamide (18, R<sub>1</sub> = *n*-Pr).** N<sup>α</sup>-Boc-ε-benzyl-D-glutamic acid (**17**, 3.37 g, 10.0 mmol) was dissolved in methylene chloride and 1.11 g (11.0 mmol) of di-*n*-propylamine and 2.11 g (11.0 mmol) of EDC were added to it. The solution was stirred until no further reaction was observed by TLC with the pH remaining ≥8.5. The reaction solution was then extracted with 0.5 M citric acid, 1 N sodium bicarbonate and water, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by silica gel flash chromatography, eluting with 97/3 CH<sub>2</sub>Cl<sub>2</sub>/MeOH. A colorless oil (2.14 g, 51%), which crystallized on standing, was obtained.

**ε-Benzyl-D-glutamic Acid Dipropylamide Hydrochloride (19, R<sub>1</sub> = *n*-Pr).** The purified N<sup>α</sup>-Boc-ε-Bzl-D-glutamic acid dipropylamide (**18**, 2.6 g, 6.2 mmol) was dissolved in 40 mL of ethyl acetate and cooled to -25 °C in a dry ice/2-propanol bath. Nitrogen was bubbled into the solution until a nitrogen atmosphere was achieved, and hydrogen chloride gas was then bubbled into the solution until the saturation point was reached. After stirring for 20 min -25 °C, nitrogen was flushed through the solution, and the solution was then concentrated in vacuo. The resultant oil solidified after standing in the refrigerator overnight to yield 1.96 g (89%).

**(R)-5-(Dipropylamino)-4-[(1*H*-indol-2-ylcarbonyl)-amino]-5-oxo-1-(phenylmethoxy)pentanoic Acid (5).** Compound **19** (R<sub>1</sub> = *n*-Pr) (1.8 g, 5.0 mmol) was dissolved in 20 mL of CH<sub>2</sub>Cl<sub>2</sub>, and the solution was cooled to 0 °C, after which 0.99 g (5.5 mmol) of indole-2-carbonyl chloride in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> was added. Triethylamine (1.11 mL, 1.1 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was added to adjust the pH to between 9 and 10, and the reaction mixture was stirred overnight. The reaction mixture was chromatographed on a silica gel flash chromatography column eluting

Table II. Physical Data for Compounds of Table I

no.	formula <sup>a</sup>	mp, °C	% purity (HPLC)	MS molecular ion	anal.
3	C <sub>20</sub> H <sub>27</sub> N <sub>3</sub> O <sub>4</sub> ·0.25H <sub>2</sub> O	110–115	98	374 (M + H)	C, H, N
4	C <sub>20</sub> H <sub>27</sub> N <sub>3</sub> O <sub>4</sub> ·0.4C <sub>3</sub> H <sub>8</sub> O	133–136	98	373	C, H, N
5	C <sub>27</sub> H <sub>33</sub> N <sub>3</sub> O <sub>4</sub>	88	99.9	464 (M + H)	C, H, N
6	C <sub>24</sub> H <sub>35</sub> N <sub>3</sub> O <sub>4</sub> ·0.51K	115–123	100	468 (M + K)	C, H, N
7	C <sub>26</sub> H <sub>35</sub> N <sub>3</sub> O <sub>4</sub> ·1.10H <sub>2</sub> O	228–230	100	454 (M + H)	C, H, N
8	C <sub>33</sub> H <sub>41</sub> N <sub>3</sub> O <sub>4</sub>	<i>b</i>	100	545 (M + H)	C, H, N
9	C <sub>22</sub> H <sub>34</sub> ClN <sub>3</sub> O <sub>4</sub> ·0.85CH <sub>4</sub> O	168–171	99	440 (M + H)	C, H, N
10	C <sub>26</sub> H <sub>40</sub> ClN <sub>3</sub> O <sub>4</sub>	<i>b</i>	98	530 (M + H)	C, H, N
11	C <sub>24</sub> H <sub>38</sub> ClN <sub>3</sub> O <sub>4</sub> ·0.1CHCl <sub>3</sub>	<i>b</i>	98	468 (M + H)	C, H, N
12	C <sub>26</sub> H <sub>41</sub> ClN <sub>3</sub> O <sub>3</sub>	<i>b</i>	>99	493 (M + H)	C, H, N <sup>c</sup>
13	C <sub>23</sub> H <sub>37</sub> N <sub>3</sub> O <sub>5</sub>	<i>b</i>	99	436 (M + H)	C, H, N
14	C <sub>23</sub> H <sub>37</sub> N <sub>3</sub> O <sub>5</sub> ·0.53H <sub>2</sub> O	<i>b</i>	>99	436 (M + H)	C, H, N
15	C <sub>27</sub> H <sub>44</sub> N <sub>4</sub> O <sub>4</sub> ·1.17H <sub>2</sub> O	<i>b</i>	97	489 (M + H)	C, H, N
16	C <sub>27</sub> H <sub>44</sub> N <sub>4</sub> O <sub>4</sub> ·1.5H <sub>2</sub> O	<i>b</i>	97	489 (M + H)	C, H, N

<sup>a</sup> NMR spectra are in agreement with all assigned structures. <sup>b</sup> Compound was obtained as an oil. <sup>c</sup> C: calcd, 63.33; found, 62.77.

with 98:2 CH<sub>2</sub>Cl<sub>2</sub>/MeOH to yield 1.52 g (66%) of crystalline 5.

(*R*)-5-(Dipropylamino)-4-[(1*H*-indol-2-ylcarbonyl)-amino]-5-oxopentanoic Acid (4). Compound 5 (841 mg) was dissolved in 30 mL of methanol, and a solution of 7.5 mL of 50% aqueous acetic acid was added. This solution, in turn, was added to 100 mg of Pd/C in a small Parr shaker flask, during flushing with nitrogen. The mixture was shaken under H<sub>2</sub> on a Parr shaker overnight followed by filtration of catalyst and evaporation of solvent. The residue was dissolved in acetone and then brought to the cloud point with hexane, with crystals beginning to form after about 1 h at room temperature. The mixture was then stored at 0 °C for 4 days, after which the crystals were filtered and analyzed. Yield: 474 mg, 70%.

*N*<sup>α</sup>-Boc-ε-benzyl-DL-glutamic Acid Dipentylamide (18, R<sub>1</sub> = *n*-pentyl). With use of the method for the synthesis of 18 (R<sub>1</sub> = *n*-Pr), 1.35 g (4 mmol) of *N*<sup>α</sup>-Boc-ε-benzyl-DL-glutamic acid, 0.843 g (4.4 mmol) of EDC, and 0.692 g (0.89 mL, 4.4 mmol) of dipentylamine were used as reagents. The product was purified on a silica gel column with chloroform as the elution solvent, resulting in 0.92 g (48%) of product as an oil.

ε-Benzyl-DL-glutamic Acid Dipentylamide Hydrochloride (19, R<sub>1</sub> = *n*-pentyl). Compound 18 from the preceding step (0.92 g, 1.93 mmol) was dissolved in 60 mL of ethyl acetate and de-blocking was carried out as described for the synthesis of 19 (R<sub>1</sub> = *n*-Pr). The solution was then flushed with nitrogen and evaporated to an oily residue (0.6 g, 75%).

(*RS*)-4-[[[(4-Chlorophenyl)amino]carbonyl]amino]-5-(dipentylamino)-5-oxo-1-(phenylmethoxy)pentanoic Acid (10). Compound 19 from the preceding step (0.6 g, 1.60 mmol) was dissolved in dry THF (25 mL), triethylamine was added to neutralize the HCl salt, and 0.223 g (1.45 mmol) of *p*-chlorophenyl isocyanate was added. The reaction was protected from moisture and stirred at room temperature for 24 h, after which the reaction mixture was placed on a silica gel column and purified by flash chromatography. The product fractions were combined and evaporated to yield 640 mg (84%) of 10.

(*RS*)-4-[[[(4-Chlorophenyl)amino]carbonyl]amino]-5-(dipentylamino)-5-oxopentanoic Acid (9). Benzyl ester 10 (1.09 g, 2.1 mmol) was dissolved in THF (31 mL) and water (17 mL), after which 2.5 N NaOH (1.5 mL total) was added in aliquots. When TLC indicated the reaction was complete, it was acidified to pH 3 with 2 N HCl and concentrated in vacuo. The product

crystallized from the more concentrated solution, and it was filtered and dried to yield 906 mg (85%) of 9.

(*RS*)-4-[[[(4-Chlorophenyl)amino]carbonyl]amino]-5-(dipentylamino)-5-oxo-1-pyrrolidinopentanoic Acid (12). Compound 9 (100 mg, 0.23 mmol) was dissolved in 2 mL of DMF, and EDC (50 mg, 0.26 mmol) was added. The mixture became homogeneous after treatment with 4 drops of pyrrolidine and was stirred at room temperature for 48 h. The reaction mixture was concentrated and the product was purified on preparative Analtch 2-μm silica gel plates, developing twice with 95:5 CHCl<sub>3</sub>/MeOH. The yield of 12 was 41 mg (37%).

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**Registry No.** 1, 6620-60-6; 2, 97964-56-2; 3, 116311-83-2; 4, 116311-84-3; 5, 117997-59-8; 6, 118100-24-6; 6-K, 123540-74-9; 7, 117997-63-4; 8, 117997-62-3; 9, 117997-60-1; 10, 117997-61-2; 11, 123540-70-5; 12, 123540-71-6; 13, 116311-87-6; 14, 116311-86-5; 15, 123540-72-7; 16, 123540-73-8; L-17, 13574-13-5; D-17, 35793-73-8; DL-17, 117997-81-6; (S)-18 (R<sub>1</sub> = Pr), 117997-74-7; (R)-18 (R<sub>1</sub> = Pr), 117997-80-5; (R)-18 (R<sub>1</sub> = *n*-pentyl), 117997-77-0; (R)-18 (R<sub>1</sub> = cyclohexyl), 123540-75-0; (RS)-18 (R<sub>1</sub> = *n*-pentyl), 118100-26-8; (S)-18 (R<sub>1</sub> = *n*-pentyl), 123620-03-1; (S)-19 (R<sub>1</sub> = Pr), 117997-75-8; (R)-19 (R<sub>1</sub> = Pr), 117997-76-9; (R)-19 (R<sub>1</sub> = *n*-pentyl), 117997-78-1; (R)-19 (R<sub>1</sub> = cyclohexyl), 117997-79-2; (RS)-19 (R<sub>1</sub> = *n*-pentyl), 118100-27-9; (S)-19 (R<sub>1</sub> = *n*-pentyl), 122742-47-6; (S)-20 (R<sub>1</sub> = Pr, R<sub>2</sub> = 2-indolyl), 117997-73-6; (R)-20 (R<sub>1</sub> = *n*-pentyl, R<sub>2</sub> = 2-indolyl), 122667-52-1; (S)-21 (R<sub>1</sub> = *n*-pentyl, Ar = 3-MeOC<sub>6</sub>H<sub>4</sub>), 123540-76-1; (R)-21 (R<sub>1</sub> = *n*-pentyl, Ar = 3-MeOC<sub>6</sub>H<sub>4</sub>), 123540-77-2; CCK, 9011-97-6; Pr<sub>2</sub>NH, 142-84-7; [H<sub>3</sub>C(CH<sub>2</sub>)<sub>4</sub>]<sub>2</sub>NH, 2050-92-2; (c-C<sub>6</sub>H<sub>11</sub>)<sub>2</sub>NH, 101-83-7; 4-ClC<sub>6</sub>H<sub>4</sub>NCO, 104-12-1; 3-MeOC<sub>6</sub>H<sub>4</sub>NCO, 18908-07-1; 2-indolyl carbonyl chloride, 7135-31-1; pyrrolidine, 123-75-1.

**Supplementary Material Available:** Table listing analysis data for compounds 3–16 (1 page). Ordering information is given on any current masthead page.