A Potent, Orally Bioavailable Benzazepinone Growth Hormone Secretagogue

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The identification of L-739,943 (**8b**), a potent, orally bioavailable benzolactam growth hormone secretagogue, is obtained from zwitterionic L-692,429 through modification of its amino acid side chain and replacement of the acidic 2′-tetrazole with the neutral and potency enhancing 2′-(*N*-methylaminocarbonylamino)methyl substituent. L-739,943 is orally active for the release of growth hormone in beagle dogs at doses as low as 0.5 mg/kg. Oral bioavailability in dogs of **8b** is 24% at a dose of 2 mg/kg with a mean drug C_{max} of 145 ± 46 ng/mL. L-739,943 represents a significant breakthrough in terms of both potency and oral bioavailability as compared to the prototype benzolactam L-692,429.

Introduction

Growth hormone (GH) release from the pituitary in mammals was originally thought to be regulated by growth hormone releasing hormone (GHRH) and somatostatin, which are both secreted from the hypothalamus.[1] Peptidomimetic growth hormone secretagogues[2−4] have recently been identified as novel mediators of growth hormone release in mammals by an alternate mechanism.[5,6] The breakthrough discovery of several growth hormone releasing peptides (GHRP's)[7] led to a search for nonpeptidyl, small molecule mimetics of the extensively studied hexapeptide GHRP-6 (His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2). The first nonpeptidyl GH secretagogue,[8,9] zwitterionic L-692,429 (**1**, Figure 1), was shown to be well tolerated and effective in stimulating GH release in humans after intravenous administration.[10] The search for an orally active growth hormone secretagogue led to the identification of MK-0677 (**2**) from a new structural class.[11] MK-0677 (**2**) has been shown to be orally efficacious for the release of growth hormone in humans[12] and is being studied in the clinic for a variety of therapeutic uses.

The prototype benzolactam secretagogue **1** has extremely low oral bioavaibility in rats and dogs. Since the molecule is zwitterionic in nature, its poor oral bioavailability was presumably attributed to poor oral absorption. In earlier reports from this laboratory,[13] we have described several replacements of the acidic 2′-tetrazole moiety of L-692,429. These neutral 2′-replacements, most notably the 2′-carboxamide,[14] gave orally active secretagogues with potency equal to or greater than L-692,429, but were not suitable for development as oral drug candidates. We report herein the modifications and structure−activity relationships of L-692,429 which led to the identification of a potent and orally bioavailable benzolactam growth hormone secretagogue, L-739,943 (**8b**).

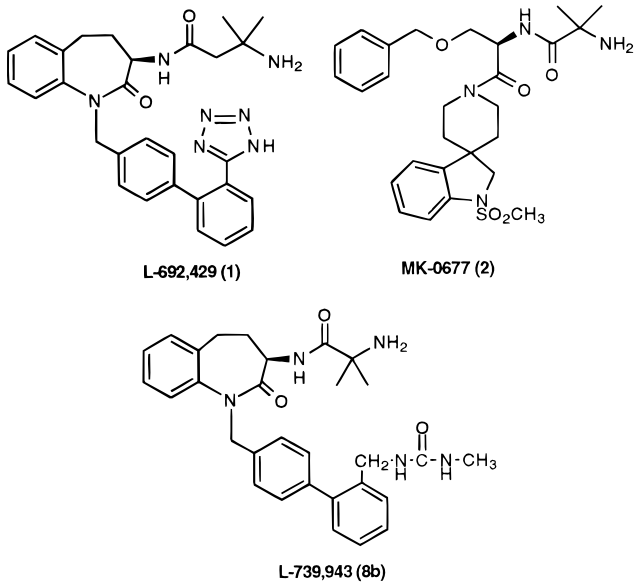

Figure 1.

Chemistry

Benzolactam growth hormone secretagogues were prepared by an approach similar to that used for L-692,429 as shown in Scheme 1. The previously described (*R*)-3-aminobenzolactam (**3**)[9] was coupled with the appropriately protected amino acid side chain (**4a**−**d**); *N*-BOC- or *N*-CBZ-3,3-dimethyl-*β*-alanine and *N*-CBZ- or *N*-BOC-2-methylalanine (α-aminoisobutyric acid, AIB) using standard amide coupling procedures. Selective deprotonation of the benzolactam nitrogen of the resulting amides **5a**−**d** and alkylation with the 2′-functionalized biphenyls **6a**−**d** afforded the framework of the benzolactam GHS structure. It was necessary to keep the temperature below 5 °C for the alkylation

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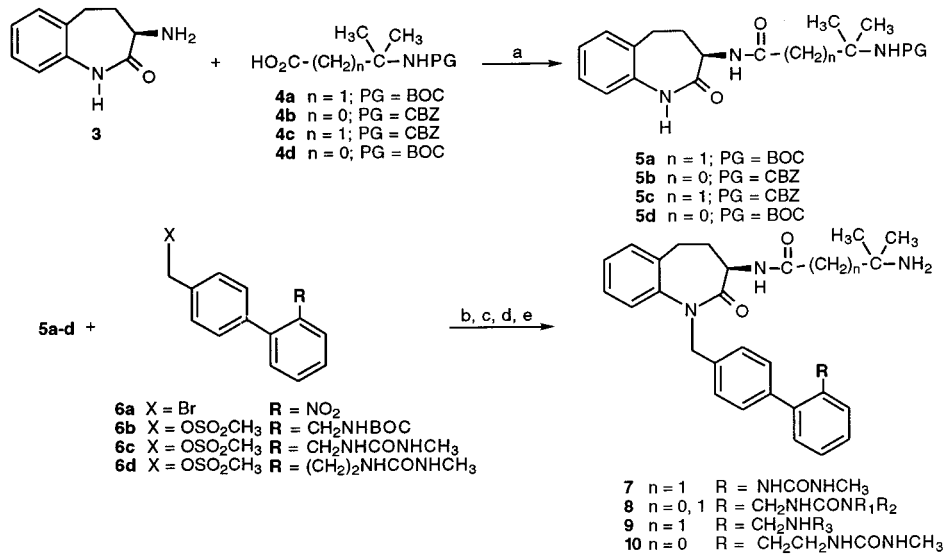
Scheme 1[a]



[a] Reagents and conditions: (a) BOP or PyBOP, TEA, CH_2Cl_2, room temperature; (b) 60% NaH, DMF, **6**, 0 °C or room temperature; (c) for NO_2, H_2 (1 atm), Pd−C, MeOH; for $(CH_2)_n$NHBOC, TFA, anisole, CH_2Cl_2, then R_1R_2NCO, R_1R_2NCOCl or R_3COCl, TEA, CH_2Cl_2; (d) for PG = BOC, TFA, anisole, CH_2Cl_2 or 9 N aqueous HCl; for PG = CBZ, H_2 (1 atom), $Pd(OH)_2$ on C, MeOH; (e) RP MPLC on C8 MeOH/0.1% aqueous TFA.

of the amides containing the AIB side chain since hydantoin formation resulted as a major byproduct at higher temperatures.

A variety of functional groups were prepared by derivatization of the 2′-position of these *N*-alkyl benzolactam intermediates. 2′-Ureas were prepared by revealing the latent amines by either nitro reduction (for **7**) or N-deprotection (for **8**) followed by reaction with the appropriate isocyanate or carbamoyl chloride. Similarly, the aminomethyl intermediate gave the acetamide derivative **9a** (R_3 = acetyl) by reaction with acetyl chloride and the 2′-amino methyl analogue **9b** (R_1 = H) by simple deprotection without nitrogen functionalization. Two urea compounds were prepared by alkylation of the amides **5a** and **5d** with the 2′-ureidobiphenyls **6c** and **6d,** respectively. Deprotection of the amino acid side chain of the resulting intermediates by hydrogenolysis with palladium hydroxide catalyst on carbon[15] for the *N*-CBZ group or acid hydrolysis (TFA or 9 N aqueous HCl) for the *N*-BOC group followed by reverse-phase medium-pressure liquid chromatography on C-8 afforded the final secretagogue products **7**, **8**, **9**, and **10** as amorphous solids.

Large-scale preparation of L-739,943 was achieved by deprotection of the intermediate containing the 2′-urea and *N*-CBZ group on the amino acid side chain by hydrogenolysis followed by addition of 1 equiv of hydrochloric acid. The crude product was crystallized from aqueous acetonitrile to afford the crystalline monohydrate HCl salt (mp 198−200 °C) which after dissolution in water and lyophilization to remove trace amounts of organic solvent provided material of high purity for biological testing.

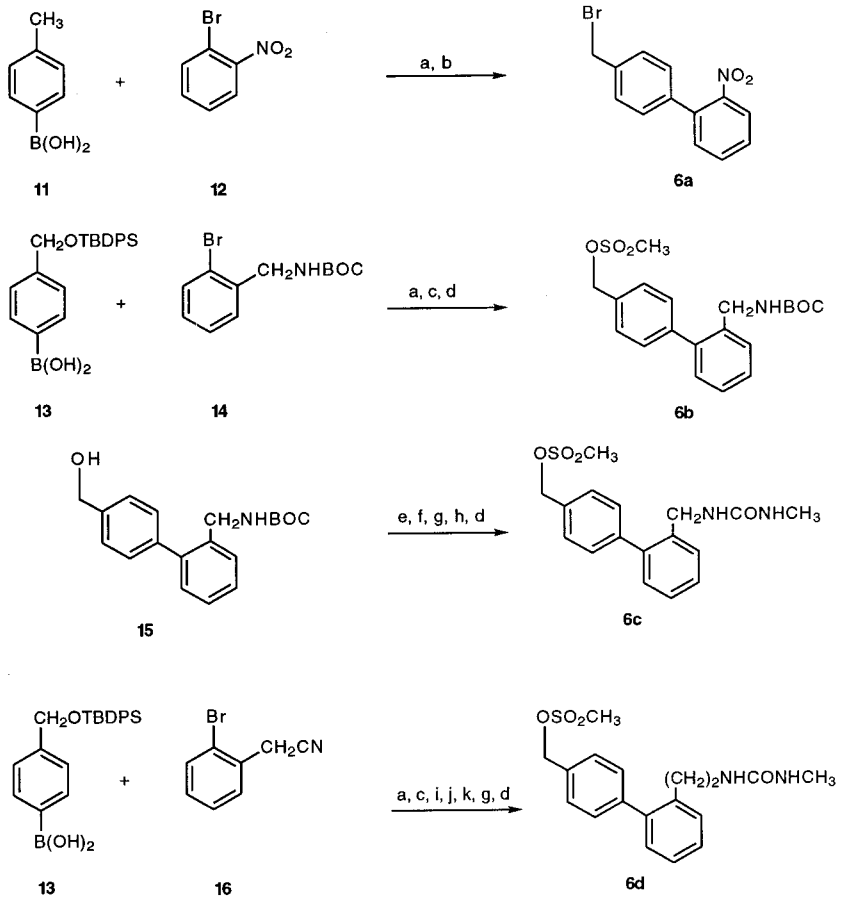
The 1,1′-biphenyl-4-methyl alkylating agents **6a**−**d** were prepared by palladium catalyzed cross-coupling of the appropriate 4-substituted aryl boronic acids with the desired 2-substituted aryl halide[16] (Scheme 2). Specifically, 4-methylphenylboronic acid (**11**) was cross-coupled with 2-nitrobromobenzene (**12**) to afford the disubstituted biphenyl in good yield. Treatment of this intermediate with NBS under radical conditions gave the desired 4-bromomethyl-2′-nitrobiphenyl (**6a**). The 2′-protected *N*-BOC amine was prepared in high yield by cross-coupling 4-(*tert*-butyldiphenylsilyloxymethyl)-phenylboronic acid (**13**), prepared in two steps from 4-bromobenzyl alcohol, with 2-*N*-BOC-aminomethyl-1-bromobenzene (**14**). Removal of the silyl protecting group and conversion to the *O*-methanesulfonate proceeded smoothly to afford the 4-methanesulfonyloxymethyl-2′-*N*-BOC-aminomethyl-1,1′-biphenyl (**6b**) in high yield.

When the neutral 2′-urea was recognized as a potent replacement of the 2′-tetrazole, two biphenyl electrophiles containing that moiety were prepared to make the synthetic sequence more convergent. The alcohol of *N*-BOC intermediate **15** was acetylated with acetic anhydride followed by deprotection of the amine with TFA. Treatment with methyl isocyanate, basic cleavage of the acetate, and conversion of the alcohol to the *O*-methanesulfonate gave the 2′-functionalized biphenyl **6c**. Preparation of the urea containing an ethylene linkage to the 2′-position was completed in a similar fashion. Cross-coupling of boronic acid **13** with 2-bromophenylacetonitrile under anhydrous conditions[17] provided the biphenylmethyl nitrile in 73% yield. Protecting group manipulation followed by nitrile reduction with tetra-*n*-butylammonium borohydride in refluxing THF and acid hydrolysis gave 2′-(2-aminoethyl)-1,1′-biphenyl-4-methanol. Selective formation of the urea with methyl isocyanate and conversion of the alcohol to the mesylate gave the eletrophilic biphenyl urea **6d**.

Results and Discussion

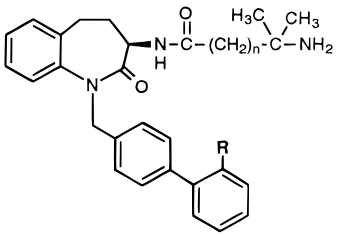
Structure−Activity Relationships. The growth hormone releasing activities of the GH secretagogues discussed are shown in Table 1. The in vitro GH releasing activities of the compounds prepared were determined using rat primary pituitary cells as previously described.[18] Potency is reported as an ED_{50}, defined as the dose at which a 50% maximal GH

Scheme 2[a]



[a] Reagents and conditions: (a) cat. $Pd(PPh_3)_4$, toluene, 2-propanol, 5 N NaOH, reflux; (b) NBS, cat. AlBN, CCl_4, reflux; (c) Bu_4NF, THF, room temperature; (d) CH_3SO_2Cl, TEA, CH_2Cl_2, 0 °C; (e) Ac_2O, TEA, CH_2Cl_2; (f) TFA, anisole, CH_2Cl_2; (g) TEA, CH_3NCO, CH_2Cl_2; (h) LiOH, aqueous THF, room temperature; (i) TBDPSCl, imidazole, DMF, room temperature; (j) Bu_4NBH_4, THF, reflux; (k) 6 N HCl, THF, reflux.

Table 1. Growth Hormone Secretagogue Activity in Vitro[a]



compd no.	R	*n*	formula	analysis	ED_{50} (nM)
1	5-(1*H*)-tetrazolyl	1	$C_{29}H_{30}N_6O_2$	CHN	60
17	5-(1*H*)-tetrazolyl	0	$C_{28}H_{28}N_6O_2$	CHN	30
18	$CONH_2$	1	$C_{29}H_{32}N_4O_3$	CHN	80
9a	$CH_2NHCOCH_3$	1	$C_{31}H_{36}N_4O_3$	CHN	200
9b	CH_2NH_2	1	$C_{29}H_{34}N_4O_2$	CHN	>1000
7	$NHCONHCH_3$	1	$C_{30}H_{35}N_5O_3$	CHN	50
8a	$CH_2NHCONHCH_3$	1	$C_{31}H_{37}N_5O_3$	CHN	6
8b	$CH_2NHCONHCH_3$ (L-739,943)	0	$C_{30}H_{35}N_5O_3$	CHN	1
8c	$CH_2NHCONH_2$	0	$C_{29}H_{33}N_5O_3$	CHN	21
8d	$CH_2NHCONHCH_2CH_3$	0	$C_{31}H_{37}N_5O_3$	CHN	6
8e	$CH_2NHCONHCH_2CH_2OH$	0	$C_{31}H_{37}N_5O_4$	CHN	2
8f	$CH_2NHCONHCH_2CH_2CH_3$	0	$C_{32}H_{39}N_5O_3$	CHN	144
8g	$CH_2NHCONHCH(CH_3)_2$	0	$C_{32}H_{39}N_5O_3$	CHN	270
8h	$CH_2NHCONH$-cyclopropyl	0	$C_{32}H_{37}N_5O_3$	CHN	45
8i	$CH_2NHCONHCH_2Ph$	0	$C_{36}H_{39}N_5O_3$	CHN	390
8j	$CH_2NHCON(CH_3)_2$	0	$C_{31}H_{37}N_5O_3$	CHN	60
10	$CH_2CH_2NHCONHCH_3$	0	$C_{31}H_{37}N_5O_3$	CHN	40

[a] Rat pituitary cell assay.

response in vitro was achieved. Although a receptor binding assay has been recently reported,[6] these compounds were assayed prior to the identification of the GHS receptor. Several compounds of historical interest have been included in the Table for completeness. The parent tetrazole compound **1**, L-692,429, has an in vitro potency of 60 nM,[9] while analogue **17**, possessing the shorter 2-methyl alanine side chain (AIB) is 2-fold more potent at 30 nM.[19] The 2′-carboxamide analogue **18**, a neutral tetrazole replacement, is of similar potency to L-692,429 with an $ED_{50} = 80$ nM.[14]

Our search for new 2′-pharmacophores led to other neutral hydrogen bond donor or acceptor groups. A benzylic amine acetamide **9a**, a "reverse amide" analogue of **18**, is approximately 3-fold less potent with an $ED_{50} = 200$ nM while the benzylic amine analogue **9b**, with an $ED_{50} > 1000$ nM, demonstrates that a positively charged amine at this position is detrimental to potency.

Another functional group with neutral hydrogen bonding capability is the 2′-*N*-methylurea **7** which is equipotent to L-692,429 ($ED_{50} = 50$ nM). Homologation at the 2′-position to the *N*-methyl benzylic urea **8a**, led to an 8-fold increase in GH releasing activity ($ED_{50} = 6$ nM). Shortening of the amino acid side chain gave analogue **8b** (L-739,943) which has an $ED_{50} = 1$ nM, a 60-fold increase in potency as compared to the prototype benzolactam GH secretagogue, L-692,429 (**1**), and 10-fold more potent than the peptidyl secretagogue GH-RP-6 ($ED_{50} = 10$ nM).[9]

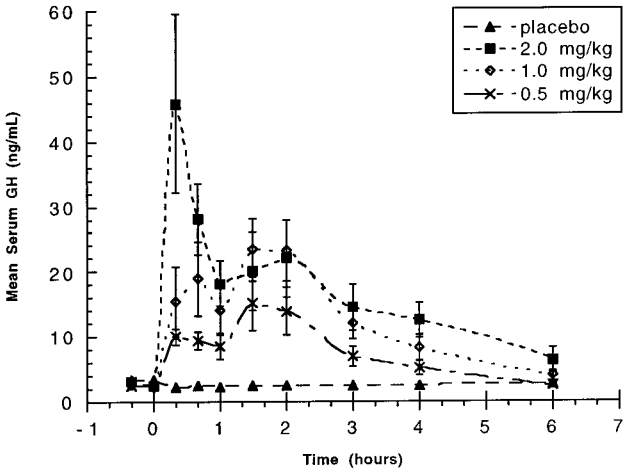


Figure 2. Geometric mean serum growth hormone levels (± within dog SE) after single oral administration of L-739,943 in beagle dogs ($n = 8$).

The structure−activity relationships of L-739,943 were explored by varying the *N*-alkyl groups of the 2′-benzylic urea. The unsubstituted urea **8c** was 21-fold less potent ($ED_{50} = 21$ nM) while substitution with an ethyl group resulted in a 6-fold decrease in GH releasing activity (**8d**, $ED_{50} = 6$ nM). Addition of a 2-hydroxyl group, to give the 2-hydroxyethyl urea **8e**, restored potency as was reported in the carboxamide series.[14] This area of the pharmacophore (receptor) is sensitive to large lipophilic groups as exemplified by the decrease in GH releasing activity for *n*-propyl analogue **8f** ($ED_{50} = 144$ nM) or 2-propyl analogue **8g** (270 nM) with some improvement observed for the slighly smaller cyclopropyl analogue **8h** ($ED_{50} = 45$ nM). Similarly, the bulky *N*-benzyl group was deleterious to GH releasing activity (**8i**, $ED_{50} = 390$ nM). In addition, the *N*,*N*-dimethylurea **8j** ($ED_{50} = 60$ nM) was 60-fold less active than the monomethyl analogue **8b** which is similar to the decrease observed for the carboxamide series previously described.[14]

The homologous urea **10** ($ED_{50} = 40$ nM), containing an ethylene group between the 2′-position of the biphenyl and the *N*-methyl urea, was 40-fold less potent than **8b**, indicating the distance of the urea moiety from the 2′-position is important for interaction of this pharmacophore with the GHS receptor (cf. **8b** ≪ **10** ≈ **7**).

In Vivo Efficacy and Oral Bioavailability of L-739, 943 (8b) in Beagle Dogs. The efficacy of L-739,943 was evaluated orally in beagle dogs in a dose range study with crossover design. Beagle dogs have proven to be a good animal model of efficacy in humans based on clinical studies with MK-0677. L-739,943 was orally effective for the release of growth hormone at doses as low as 0.5 mg/kg with a dose dependent increase in GH levels observed for over 2 h postdosing (Figure 2). Mean GH peak levels at 1.0 and 2.0 mg/kg doses ranged from 8.3 to 74.6 and 35.7 to 188.4 ng/mL, respectively. Likewise, the GH AUC (0−6 h) was 83.9 and 107.8 ng h/mL, respectively. The GH response was biphasic in 14 of 24 dogs dosed with the first peak occurring at 20 or 40 min and a second peak at 1.5 or 2 h postdosing. The mean serum GH AUC (0−6 h) levels increased 3.5-, 5.4-, and 7.0-fold over control in a dose dependent manner. These results compare favorably with MK-0677, which though orally active at a lower dose (0.25 mg/kg) produces a similar GH response to that obtained with L-739,943 at a dose of 0.5 mg/kg.[11]

The specificity of L-739,943 for the release of GH was evaluated in comparison to cortisol, insulin-like growth factor 1 (IGF-1), prolactin, luteinizing hormone, and thryroxine release. At a dose of 1.0 mg/kg with GH AUC(0−6 h) increased by 5.4-fold, cortisol AUC (0−6 h) was increased 2.5-fold while prolactin, lutenizing hormone, and thyroxine were not significantly altered. IGF-1 levels were increased by 32% at 6 h at this dose. The increase in cortisol has been observed with other nonpeptidyl[8,11] and peptidyl GH secretagogues,[20] and it is still unclear whether this effect is related to its novel mechanism of action or whether it is of any clinical significance.

Comparison of plasma concentration after iv dosing at 0.2 mg/kg and oral dosing at 2 mg/kg of body weight determined the oral bioavailability and pharmacokinetics of L-739,943 in beagle dogs. L-739,943 gave, after an iv dose, an area under the curve (AUC) of 231 ± 61.4 ng h/mL, a clearance of 15.1 ± 4.0 mL/min/kg, and a half-life of 2.4 ± 0.5 h. When dosed orally, C_{max} was 145.1 ± 46.4 ng/mL and the AUC was 528.3 ± 16.5 ng h/mL. The bioavailability in beagle dogs based on these data was estimated to be 23.8 ± 5.7% ($n = 3$, range 18.1−29.5%) assuming linear kinetics for the two different doses. L-739,943 is significantly more orally bioavailable than the parent benzolactam compound L-692,429 which was only 2% bioavailable in dogs.[21]

Conclusion

We have reported the chemistry and biology of an orally active benzolactam GH secretagogue L-739,943 (**8b**). The earlier benzolactam secretagogue L-692,429 was improved upon by key modifications of the amino acid side chain and the 2′-tetrazole which removed its zwitterionic nature. The critical positioning of the methylurea moiety, a neutral tetrazole replacement, from the 2′-biphenyl removed the ionic charge and substantially increased potency. Similarly, potency was also improved by use of the shortened amino acid side chain which resulted in a decrease in basicity of this amine (pK_a changes from 9.2 to 7.5). The combination of these changes resulted in a 60-fold increase in potency in vitro compared to the parent compound L-692,429. The zwitterionic L-692,429 has been converted to a near neutral compound at physiological pH which improved the oral absorption and bioavailability of L-739,943.

L-739,943 has an intrinsic in vitro potency of 1 nM in the rat pituitary cell assay which is equipotent to MK-0677 (**2**). Oral efficacy of compound **8b** was demonstrated in beagle dogs with a dose dependent GH release observed at doses as low as 0.5 mg/kg and a maximum serum GH level of 188 ng/mL at a dose of 2 mg/kg. Oral bioavailability in beagle dogs was determined to be 23.8% with a C_{max} of 145 ng/mL, a large AUC of 528 ng h/mL after oral administration at 2 mg/kg. The GH response in beagle dogs for L-739, 943 at oral doses from 0.5 to 2.0 mg/kg compare favorably to that of MK-0677 at similar doses even though the oral bioavailability of L-739,943 is approximately 3-fold lower.

Experimental Section

Chemistry. General Methods. ^{1}H NMR spectra were recorded on Varian XL series spectrometers at the indicated field strengths. Low-resolution mass spectral analyses were obtained with a LKB 9000 at an ionizing voltage of 70 eV. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter at ambient temperature. Reagents, solvents, and drying agents were obtained from commercial sources and used without further purification or drying unless stated otherwise. GHRP-6 was obtained from BACHEM Bioscience, Inc., Philadelphia, PA, custom synthesis lot ZF892. Rat GRF was obtained from Sigma Chemical Co., St. Louis, MO. Normal phase column chromatography was carried out utilizing silica gel 60 (E. Merck). Preparative reverse phase medium-pressure liquid chromatography was carried out with Lobar LiChroprep C-8 (E. Merck) prepacked columns. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

***N*-[1-[[2′-[(Methylaminocarbonyl)amino][1,1′-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3(*R*)-yl]-3-amino-3-methylbutanamide, trifluoroacetate (7). 3-*tert*-Butoxycarbonylamino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3(*R*)-yl]-butanamide (5a).** A solution of 8.70 g (49.4 mmol) of 3(*R*)-amino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**3**) in 100 mL of methylene chloride was treated with 10.73 g (49.4 mmol) of 3-*tert*-butoxycarbonylamino-3-methylbutanoic acid (**4a**) and 13.8 mL of triethylamine (10.0 g, 99 mmol, 2 equiv). The reaction flask was immersed in an ambient temperature water bath. Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (26 g, 59 mmol, 1.2 equiv) was added and the mixture stirred at room temperature for 2 h. The reaction mixture was added to 300 mL of ethyl acetate and washed three times with 5% aqueous citric acid, twice with saturated aqueous sodium bicarbonate, and once with saturated aqueous sodium chloride. The organic layer was removed, dried over magnesium sulfate, and filtered and the filtrate concentrated under vacuum. The residue was purified by preparative high-pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (4:1), to afford 17.42 g (46.4 mmol, 94%) of product **5a** as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 6H), 1.44 (s, 9H), 1.95 (m, 1H), 2.46 (d, 15 Hz, 1H), 2.59 (d, 15 Hz, 1H), 2.6−3.0, (m, 3H), 4.53 (m, 1H), 5.30 (br s, 1H), 6.72 (d, 7 Hz, 1H), 6.98 (d, 8 Hz, 1H), 7.1−7.3 (m, 3H), 7.82 (br s, 1H). FAB-MS: calculated for $C_{20}H_{29}N_3O_4$ 375; found 376 (M + H,70%).

4-Methyl-2′-nitro-1,1′-biphenyl. A vigorously stirred mixture of 4-tolylboronic acid (34 g, 0.25 mol) and 2-bromo-1-nitrobenzene (34 g, 0.168 mol) in a mixture of 5 *N* sodium hydroxide (170 mL), water (57 mL), 2-propanol (215 mL), and benzene (1080 mL) under a nitrogen atmosphere was treated with tetrakis(triphenylphosphine)palladium(0) (11.9 g). The stirred bilayer reaction mixture was heated at reflux for 3 h. The cooled reaction mixture was filtered through Celite and the filter cake washed with fresh benzene. The organic layer was separated and washed with water (3×), dried over magnesium sulfate, and filtered. The filtrate was evaporated under vacuum and the residue (46.1 g) purified by preparative high-pressure liquid chromatography on silica gel, eluting with hexane/ethyl acetate (20:1), gave 28.05 g of product **6a**. EI-MS: calculated for $C_{13}H_{11}NO_2$ 213; found 213 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 7.20 (m, 4H), 7.43 (m, 2H), 7.59 (t, 1H), 7.8 (d, 1H).

4-Bromomethyl-2′-nitro-1,1′-biphenyl (6a). A solution of 4-methyl-2′-nitro-1,1′-biphenyl (6.0 g, 28.2 mmol), *N*-bromosuccinimide (4.99 g, 28.2 mmol), and AIBN (653 mg) in 75 mL of carbon tetrachloride was heated at reflux until a negative potassium iodide test was obtained (1.5 h). The reaction mixture was cooled and filtered. The filtrate was evaporated under vacuum to yield 8.41 g of crude product. ^{1}H NMR revealed the product composition was approximately 75% monobromo and 10% dibromo, in addition to 15% of unreacted starting material. The crude product was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.53 (s, 2H), 7.2−7.7 (m, 7H), 7.85 (m, 1H). EI-MS: calculated for $C_{14}H_{10}BrN$ 272; found 272,274 (M^+).

***N*-[1-[[(2′-Nitro)[1,1′-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3(*R*)-yl]-3-*tert*-butoxycarbonylamino-3-methylbutanamide.** A solution of 1.28 g (3.4 mmol) of 3-*tert*-butoxycarbonylamino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3(*R*)-yl]butanamide (**5a**) in 6 mL of dry dimethylformamide was treated with 163 mg of 60% sodium hydride oil dispersion (4.07 mmol). The reaction mixture was stirred at room temperature for 30 min. To the solution was added 1.0 g (3.4 mmol) of solid 4-bromomethyl-2′-nitro-1,1′-biphenyl (**6a**). After stirring at room temperature for 4 h, the reaction mixture was diluted with 200 mL of ethyl acetate. The organic layer was washed with water (4 × 50 mL), dried over magnesium sulfate, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:1) to give 1.81 g (90%) of the product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 6H), 1.41 (s, 9H), 1.83 (m, 1H), 2.35−2.70 (m, 5H), 4.50 (m, 1H), 4.84 (d, 15 Hz, 1H), 5.23 (d, 15 Hz, 1H), 5.27 (s, 1H), 6.64 (d, 7 Hz, 1H), 7.1−7.6 (m, 11H), 7.80 (d, 8 Hz, 1H). FAB-MS: calculated for $C_{33}H_{38}N_4O_6$ 586; found 587 (M + H).

***N*-[1-[[(2′-Amino)[1,1′-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3(*R*)-yl]-3-*tert*-butoxycarbonylamino-3-methylbutanamide.** A solution of 7.79 g (13.23 mmol) of the intermediate obtained above in 200 mL of methanol containing 0.9 g of 5% palladium on carbon was hydrogenated at 40 psi. When the uptake of hydrogen was complete, the catalyst was removed by filtration through Celite. The filtrate was concentrated under vacuum to yield 6.6 g (11.9 mmol, 90%) of product. FAB-MS: calculated for $C_{33}H_4N_4O_4$ 556; found 557 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 6H), 1.39 (s, 9H), 1.87 (m, 1H), 2.51 (dd, 1H), 2.59 (m, 1H), 4.51 (m, 1H), 4.89 (d, 1H), 5.15 (d, 1H), 5.32 (br s, 1H), 6.71 (d, 1H), 6.81 (s, 1H), 7.21 (m, 10H).

***N*-[1-[[2′-[(Methylaminocarbonyl)amino][1,1′-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3(*R*)-yl]-3-*tert*-butoxycarbonylamino-3-methylbutanamide.** A solution of 88.4 mg (0.158 mmol) of the intermediate obtained above in 4 mL of methylene chloride at room temperature was treated with 0.5 mL of methyl isocyanate (8.5 mmol). The reaction mixture was stirred at room temperature for 18 h, when all starting material was consumed as indicated by thin-layer chromatography. The reaction was evaporated under vacuum and the residue passed over silica gel. Elution with ethyl acetate/*n*-hexane (3:1) yielded 66 mg (0.11 mmol, 68%) of product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.23 (s, 3H), 1.39 (s, 9H), 1.89 (m, 1H), 2.49 (dd, H), 2.60 (m, 2H), 2.69 (s, 3H), 4.50 (m, 1H), 4.95 (d, 1H), 5.06 (d, 1H), 5.26 (br s, 1H), 6.24 (br s, 1H), 6.70 (d, 1H), 7.22 (m, 11H), 7.71 (d, 1H).

***N*-[1-[[2′-[(Methylaminocarbonyl)amino][1,1′-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3(*R*)-yl]-3-amino-3-methylbutanamide, trifluoroacetate (7).** A solution of 66 mg (0.11 mmol) of the intermediate obtained above in 2 mL of methylene chloride was treated with 2 mL of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 1 h, when thin-layer chromatography indicated that no starting material remained. The reaction mixture was evaporated to dryness under vacuum, and the residue was purified by medium-pressure liquid chromatography on C8, eluting with methanol/0.1% aqueous trifluoroacetic acid (60:40). Fractions containing the product were combined and evaporated under vacuum, and the residue was lyophilized from water to give 26 mg (0.051 mmol, 46%) of the title compound as a white solid. FAB-MS: calculated for $C_{30}H_{35}N_5O_3$ 513; found 536 (M + Na). ^{1}H NMR (400 MHz, CD_3OD): δ 1.34 (s, 3H), 1.37 (s, 3H), 2.13 (m, 1H), 2.39 (m, 1H), 2.54 (dd, 1H), 2.63 (s, 3H), 3.29 (dd, 1H), 4.95 (d, 1H), 5.11 (d, 1H), 7.22 (m, 10H), 7.60 (d, 1H).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(methylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]-methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Hy-

drochloride (8b, L-739,943). 2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide (5b). Prepared from *N*-carbobenzyloxy-2-methylalanine (**4b**) and 3(R)-amino-2,3,4,5-tetrahydro-1*H*-benzazepin-2-one (**3**) substituting benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate for benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate according to the procedure described for **5a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 3H), 1.52 (s, 3H), 1.82 (m, 1H), 2.50−3.00 (m, 3H), 4.45 (m, 1H), 5.05 (s, 2H), 5.37 (s, 1H), 6.80−7.40 (m, 10H), 8.65 (s, 1H). FAB-MS: calculated for $C_{22}H_{25}N_3O_4$ 395; found 396 (M + H,100).

4-Bromobenzyl *tert*-Butyldiphenylsilyl Ether. To a solution of 28.2 g (0.150 mol) of 4-bromobenzyl alcohol in 470 mL of dry dimethylformamide under nitrogen atmosphere was added 31.4 mL (0.225 mol) of triethylamine. The reaction mixture was cooled to 0 °C, and 43 mL (0.17 mol) of *tert*-butylchlorodiphenylsilane was added dropwise by addition funnel. The reaction mixture was stirred at ambient temperature overnight and then poured into a separatory funnel containing 1 L of diethyl ether and 500 mL of water. To this mixture was added 125 mL of 2 N aqueous hydrochloric acid. The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 350 mL). The organic extracts were combined, washed with water (2 × 250 mL), and dried over magnesium sulfate. The solids were removed by filtration, and the solvent was removed under vacuum to give an oil which crystallized on standing. The flask containing the crude product was placed in the freezer overnight and then triturated with a minimal amount of methanol and filtered. The solid was air-dried for several hours and then dried under vaccuum overnight to afford 59.5 g (93%) of product as an off-white solid (mp 44−47 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (s, 9H), 4.76 (s, 2H), 7.25 (d, 8 Hz, 2H), 7.45 (m, 8H), 7.75 (m, 4H). FAB-MS: calculated for $C_{23}H_{25}BrOSi$ 424; found 425 (M+H, 7%).

4-(*tert*-Butyldiphenylsiloxymethyl)phenylboronic Acid (13). To a solution of 20 g (47 mmol) of 4-bromobenzyl *tert*-butyldiphenyl silyl ether in 200 mL of dry tetrahydrofuran under a nitrogen atmosphere at −78 °C was added dropwise by syringe 19.74 mL (49.35 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes over 20 min. The resulting mixture was stirred for 30 min, and then 11.6 mL (50.3 mmol) of triisopropyl borate was added by syringe. The reaction mixture was stirred at −78 °C for 30 min and then slowly warmed to room temperature and stirred for an additional 2 h. The reaction mixture was then quenched by the addition of 750 mL of water containing 100 mL of concentrated hydrochloric acid and 500 mL of diethyl ether. The mixture was strirred for 1 h, and then the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 400 mL). The combined ether extracts were washed with saturated aqueous sodium chloride (4 × 100 mL), dried over magnesium sulfate, and filtered. The solvent was removed under vacuum to give an oil which was crystallized by dissolving in hexanes and evaporation of the solvent under vacuum to afford 15.6 g (85%) of a white solid (mp 171−174 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 (s, 9H), 4.86 (s, 2H), 7.40 (m, 6H), 7.58 (d, 8 Hz, 2H), 7.70 (m, 4H), 8.22 (d, 8 Hz, 2H). FAB-MS: calculated for $C_{23}H_{27}BrO_3Si$ 390; found 372 (M − H_2O).

***N*-(*tert*-Butoxycarbonyl)-2-bromobenzylamine (14).** To a slurry of 8.88 g (39.9 mmol) of 2-bromobenzylamine hydrochloride in 100 mL of dry methylene chloride under a nitrogen atmosphere was added by syringe 12.24 mL (87.80 mmol) of triethylamine. The resulting solution was stirred at 0 °C for 5 min and then treated with 9.6 g (44 mmol) of di-*tert*-butyl dicarbonate. The reaction was stirred at room temperature for 2 h and then diluted with 350 mL of methylene chloride. The solution was washed with water (2 × 150 mL), saturated aqueous ammonium chloride (150 mL), saturated aqueous sodium bicarbonate (4 × 150 mL), and saturated aqueous sodium chloride (150 mL), dried over sodium sulfate, and filtered. The solvent was removed under vacuum to give an oil which was crystallized by dissolving in hot hexanes, filtering and cooling the solution. The product was filtered and dried under vacuum to afford 8.66 g (90%) of a white solid (mp 51−53 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 4.37 (d, 5 Hz, 2H), 5.00 (s, 1H), 7.10 (m, 1H), 7.25 (m, 1H), 7.35 (m, 1H), 7.40 (d, 6 Hz, 1H). FAB-MS: calculated for $C_{12}H_{16}BrNO_2$ 285; found 286 (M + H).

2′-[(*tert*-Butoxycarbonylamino)methyl]-4-[(*tert*-butyldiphenylsiloxy)methyl]-1,1′-biphenyl. To a solution of 3.2 g (8.2 mmol) of 4-(*tert*-butyldiphenylsilyoxymethyl)phenylboronic acid in 64 mL of benzene was added 2.2 mL of water, 6.4 mL of 5 N aqueous sodium hydroxide, and 8.3 mL of 2-propanol. To this mixture was added 180 mg (0.16 mmol) of tetrakis-(triphenylphosphine)palladium and 2.20 g (7.81 mmol) of *N*-(*tert*-butoxycarbonyl)-2-bromobenzylamine. The resulting mixture was heated under nitrogen at reflux for 2 h then cooled to room temperature. The reaction mixture was diluted with 100 mL of water, transferred to a separatory funnel, and extracted with ether (3 × 150 mL). The combined ether extracts were washed with saturated aqueous sodium bicarbonate (100 mL) and saturated aqueous sodium chloride (100 mL), dried over magnesium sulfate, and filtered. The solvent was removed under vacuum to give a crude product which was purified by column chromatography on silica gel eluting with hexanes/ethyl acetate (9:1) to afford 4.31 g (100%) of the product as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 (s, 9H), 1.41 (s, 9H), 4.27 (d, 6 Hz, 2H), 4.45 (m, 1H), 4.81 (s, 2H), 7.20−7.49 (m, 14H), 8.72 (m, 4H). FAB-MS: calculated for $C_{35}H_{41}NO_3Si$ 551; found 552 (M + H).

2′-[(*tert*-Butoxycarbonylamino)methyl]-1,1′-biphenyl-4-methanol. To a solution of 3.85 g (7.00 mmol) of 2′-[(*tert*-butoxycarbonylamino)methyl]-4-[(*tert*-butyldiphenylsiloxy)-methyl]-1,1′-biphenyl in 25 mL of dry tetrahydrofuran under a nitrogen atmosphere was added by syringe 10.5 mL (0.530 mmol) of a 1.0 M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran. The reaction mixture was stirred for 2 h and then diluted with 700 mL of diethyl ether. The mixture was washed with water (3 × 150 mL), saturated aqueous sodium bicarbonate (50 mL), and saturated aqueous sodium chloride (50 mL), then dried over magnesium sulfate, and filtered. The solvent was removed under vacuum to give an oil which was purified by column chromatography on silica gel eluting with hexanes/ethyl acetate (55:45) to afford 2.02 g (92%) of the product as a white solid (mp 89−93 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.50 (s, 2H), 4.20 (s, 2H), 4.70 (s, 2H), 7.18−7.45 (m, 8H). FAB-MS: calculated for $C_{19}H_{23}NO_3$ 313; found 314 (M + H).

2′-[(*tert*-Butoxycarbonylamino)methyl]-1,1′-biphenyl-4-methanol, Methanesulfonate Ester (6b). To a solution of 53 mg (0.17 mmol) of 2′-[(*tert*-butoxycarbonylamino)methyl]-1,1′-biphenyl-4-methanol in 1 mL of dry methylene chloride under nitrogen at 0 °C was added by syringe 0.035 mL (0.25 mmol) of triethylamine followed by 0.016 mL (0.20 mmol) of methanesulfonyl chloride. The reaction mixture was stirred for 2 h at 0 °C, diluted with 75 mL of methylene chloride, washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried over sodium sulfate, and filtered. The solvent was removed under vacuum to give 61 mg (97%) of the product as a white solid which was used in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 9H), 2.95 (s, 3H), 4.20 (d, 5 Hz, 2H), 4.65 (s, 1H), 5.25 (s, 2H), 7.18−7.50 (m, 8H). FAB-MS: calculated for $C_{20}H_{25}NO_5S$ 391; found 392 (M + H).

2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[(*tert*-butoxycarbonylamino)methyl]-[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]-propanamide. To a solution of 819 mg (2.07 mmol) of 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide (**5b**) in 7 mL of dry dimethylformamide under nitrogen at 0 °C was added 83 mg (2.1 mmol) of 60% sodium hydride/oil dispersion. After stirring for 15 min, a solution of 810 mg (2.1 mmol) of 2′-[(*tert*-butoxycarbonylamino)methyl]-1,1′-biphenyl-4-methanol, methanesulfonate ester (**6b**) in 2 mL of dimethylformamide was added by

cannula. The flask which originally contained the methanesulfonate ester was rinsed with 1 mL of dimethylformamide which was added to the reaction mixture. After 15 min of stirring at 0 °C, the reaction mixture was diluted with 400 mL of ethyl acetate and 50% saturated ammonium chloride. The mixture was transferred to a separatory funnel, and the aqueous layer was separated. The organic layer was washed with 100 mL of saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic layer was dried over magnesium sulfate and filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/hexane (55:45) to afford 1.2 g (84%) of a white foam. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 9H), 1.48 (s, 3H), 1.52 (s, 3H), 1.78 (s, 1H), 2.35−2.70 (m, 3H), 4.18 (d, 6 Hz, 2H), 4.38−4.62 (m, 2H), 4.82 (d, 16 Hz, 1H), 5.05 (s, 2H), 5.25 (d, 16 Hz, 1H), 5.32 (s, 1H), 7.08 (d, 6 Hz, 1H), 7.12−7.43 (m, 18H). FAB-MS: calculated for $C_{41}H_{46}N_4O_6$ 690; found 691(M + H).

2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide, Hydrochloride. To a solution of 9.83 g (0.55 mmol) of 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[(*tert*-butoxycarbonylamino)methyl][1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide in 170 mL of methanol was added 120 mL of 9 N aqueous hydrochloric acid. Periodically, 10 mL portions of methanol were added to the reaction mixture to dissolve precipitates which form during the reaction (50 mL total). The reaction mixture was stirred overnight at room temperature, and then the solvent was removed under vacuum. The resulting oil was dissolved in methanol, and the solvent was removed under vacuum to afford 8.57 g (96%) of the title compound as an off-white foam. ^{1}H NMR (200 MHz, CD_3OD): δ 1.40 (s, 6H), 1.90 (m, 1H), 2.20−2.65 (m, 3H), 4.02 (s, 2H), 4.32 (m, 1H), 4.96 (d, 16 Hz, 1H), 5.00 (s, 2H), 5.25 (d, 16 Hz, 1H), 7.08−7.65 (m, 17H). FAB-MS: calculated for $C_{36}H_{38}N_4O_4$ 590; found 591 (M + H, 100%).

2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(methylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide. To a solution of 8.57 g (13.7 mmol) of 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide hydrochloride in 75 mL of dry methylene chloride under nitrogen was added 2.28 mL (16.4 mmol) of triethylamine followed by 0.89 mL (15 mmol) of methyl isocyanate. After 45 min of stirring at room temperature, the solvent was removed under vacuum. The resulting material was dissolved in methylene chloride and purified by flash column chromatography on silica gel eluting with ethyl acetate/methanol (96:4) to afford 7.73 g (87%) of product as a white foam. ^{1}H NMR (200 MHz, CD_3OD): δ 1.39 (s, 6H), 1.82 (m, 1H), 2.15−2.60 (m, 3H), 2.63 (s, 3H), 4.13 (s, 2H), 4.36 (m, 1H), 4.86 (d, 15 Hz, 1H), 4.85 (s, 2H), 5.32 (d, 15 Hz, 1H), 7.08−7.43 (m, 17H). FAB-MS: calculated for $C_{38}H_{41}N_5O_5$ 647; found 648(M + H, 80%).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(methylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]-methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Hydrochloride (8b, L-739,943). To a solution of 5.00 g (7.72 mmol) of 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(methylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide in 100 mL of dry methanol was added 0.50 g (0.1 equiv by weight) of palladium hydroxide. The mixture was stirred under a hydrogen atmosphere for 2 h. The mixture was filtered through Celite. The filter pad was washed with 50 mL of methanol. The filtrate was combined, and the solvent was removed under vacuum. The resulting oil was dissolved in 50 mL of methanol and treated with 17 mL (8.5 mmol) of a 0.5 N aqueous hydrochloric acid solution. The solvent was removed under vacuum to give a solid which was crystallized by refluxing in 480 mL of acetonitrile/ethanol (7:1). The mixture was cooled to room temperature with gentle stirring. After 3 h the solids were filtered and washed with 80 mL of ice cold acetonitrile/ethanol (7:1) and then air-dried for 3 h. The resulting solid (containing trace amounts of acetonitrile; mp 198−200°) was dissolved in 40 mL of water, filtered, and lyophilized overnight to afford 3.78 g (89%) of the title compound as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.55 (s, 3H), 1.64 (s, 3H), 2.28 (m, 2H), 2.62 (m, 2H), 2.67 (s, 3H), 4.16 (dd; 16, 14 Hz; 2H), 4.39 (dd; 12, 8 Hz; 1H), 5.00 (d, 15 Hz, 1H), 5.22 (d, 15 Hz, 1H), 7.14 (d, 7 Hz, 1H), 7.20−7.41 (m, 11H). FAB-MS: calculated for $C_{30}H_{35}N_5O_3$ 513; found 514 (M + H, 100%). $[\alpha]_D = +121°$ (c = 1, methanol).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[((2-hydroxyethyl)amino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, trifluoroacetate (8e). 2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate. To a solution of 380 mg (0.55 mmol) of 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[(*tert*-butoxycarbonylamino)methyl][1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide in 2 mL of dry methylene chloride was added 5 drops of anisole followed by 2 mL of trifluoroacetic acid. The reaction mixture was stirred for 1.5 h at room temperature at which time the solvent was removed under vacuum. The resulting oil was dissolved in 5 mL of carbon tetrachloride, and the solvent was removed under vacuum. The process was repeated with 5 mL of chloroform followed by 5 mL of methylene chloride to give 427 mg (>100%) of the product containing minor amount of anisole as an off-white foam which was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 6H), 1.90 (m, 1H), 2.25−2.65 (m, 3H), 4.12 (s, 2H), 4.38 (m, 1H), 4.85 (d, 16 Hz, 1H), 4.96 (s, 2H), 5.05 (d, 16 Hz, 1H), 5.55 (s, 1H), 6.91 (m, 1H), 7.05−7.60 (m, 19H). FAB-MS: calculated for $C_{36}H_{38}N_4O_4$ 590; found 591 (M + H, 100%).

2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[((2-hydroxyethyl)amino)carbonyl]amino]-methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide. To a solution of 160 mg (0.23 mmol) of 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide trifluoroacetate in 1 mL of dry methylene chloride under nitrogen atmosphere was added 0.063 mL (0.45 mmol) of triethylamine followed by 0.039 mL (0.25 mmol) of 2-isocyanatoethyl methacrylate. The reaction mixture was stirred at room temperature for 30 min, and then the solvent was removed under vacuum.

The residue was dissolved in 2 mL of tetrahydrofuran/water (3:1), and to the resulting solution was added 42 mg (1.0 mmol) of lithium hydroxide monohydrate. After 3 h of stirring at room temperature, the reaction mixture was diluted with 100 mL of ethyl acetate and washed with 50 mL of brine. The organic layer was dried over magnesium sulfate and filtered and the solvent removed under vacuum to afford 149 mg (97%) of the product as a white foam. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (m, 9H), 1.82 (m, 1H), 2.10−2.70 (m, 3H), 3.05 (m, 2H), 3.15 (t, 4 Hz, 2H), 2.55 (t, 4 Hz, 2H), 4.20 (s, 2H), 4.45 (m, 1H), 4.68 (s, 1H), 5.03 (s, 2H), 5.38 (s, 1H), 7.05−7.43 (m, 19H). FAB-MS: calculated for $C_{39}H_{43}N_5O_6$ 677; found 678 (M + H, 60%).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[((2-hydroxyethyl)amino)-carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8e). To a solution of 149 mg (0.22 mmol) of 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[((2-hydroxyethyl)amino)carbonyl]amino]methyl]-[1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide in 3 mL of dry methanol was added 30 mg (0.2 equiv by weight) of palladium hydroxide. The mixture was stirred under a hydrogen atmosphere for 2 h. The mixture was filtered through Celite. To the filtrate was added 3 drops of trifluoroacetic acid, and the solvent was removed under vacuum to give a solid which was purified by reverse phase medium-pressure liquid chromatography on C8, eluting with

methanol/0.1% aqueous trifluoroacetic acid (60:40) to afford 87 mg (60%) of the title compound as a white solid. ^{1}H NMR (200 MHz, CD_3OD): δ 1.53 (s, 3H), 1.62 (s, 3H), 2.28 (m, 2H), 2.60 (m, 2H), 3.19 (t, 6 Hz, 2H), 3.53 (t, 6 Hz, 2H), 4.15 (s, 2H), 4.39 (dd, 12, 8 Hz; 1H), 4.99 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.10−7.41 (m, 12H). FAB-MS: calculated for $C_{31}H_{37}N_5O_4$ 543; found 544 (M + H, 80).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[(aminocarbonyl)amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8c). 2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[(aminocarbonyl)amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide. The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(R)-yl]propanamide, trifluoroacetate and trimethylsilyl isocyanate according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.40 (s, 6H), 1.82 (m, 1H), 2.15−2.60 (m, 3H), 4.12 (s, 2H), 4.32 (m, 1H), 4.85 (d, 15 Hz, 1H), 5.00 (s, 2H), 5.32 (d, 15 Hz, 1H), 7.05−7.43 (m, 17H). FAB-MS: calculated for $C_{37}H_{39}N_5O_5$ 633; found 644 (M + H, 100).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[(aminocarbonyl)amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8c). The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[(aminocarbonyl)amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(R)-yl]propanamide according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.53 (s, 3H), 1.62 (s, 3H), 2.25 (m, 2H), 2.58 (m, 2H), 4.13 (s, 2H), 4.37 (dd, 12, 8 Hz; 1H), 4.97 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.10−7.41 (m, 12H). FAB-MS: calculated for $C_{29}H_{33}N_5O_3$ 499; found 500 (M + H, 100).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(ethylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8d). 2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(ethylamino)carbonyl]amino]methyl]-[1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide. The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(R)-yl]propanamide, trifluoroacetate and ethyl isocyanate according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.03 (t, 7 Hz, 3H), 1.39 (s, 6H), 1.82 (m, 1H), 2.18−2.58 (m, 3H), 3.07 (q, 2H), 4.12 (s, 2H), 4.32 (m, 1H), 4.87 (d, 15 Hz, 1H), 5.00 (s, 2H), 5.31 (d, 15 Hz, 1H), 7.08−7.40 (m, 17H). FAB-MS: calculated for $C_{39}H_{43}N_5O_5$ 661; found 662 (M + H, 100).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(1-ethylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8d). The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(1-ethylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-*2*-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.05 (t, 7 Hz, 3H), 1.53 (s, 3H), 1.62 (s, 3H), 2.25 (m, 2H), 2.58 (m, 2H), 3.09 (q, 2H), 4.14 (s, 2H), 4.37 (dd, 11, 8 Hz; 1H), 4.97 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.10−7.41 (m, 12H). FAB-MS: calculated for $C_{31}H_{37}N_5O_3$ 527; found 528 (M + H, 100).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(1-propylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8f). 2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(1-propylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]Propanamide. The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide, trifluoroacetate and 1-propyl isocyanate according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 0.86 (t, 7.5 Hz, 3H), 1.39 (s, 6H), 1.42 (m, 2H), 1.82 (m, 1H), 2.19−2.55 (m, 3H), 3.01 (t, 7 Hz, 2H), 4.12 (s, 2H), 4.32 (m, 1H), 4.85 (d, 15 Hz, 1H), 5.00 (s, 2H), 5.31 (d, 15 Hz, 1H), 7.08−7.40 (m, 17H), 7.63 (d, 8 Hz, 1H). FAB-MS: calculated for $C_{40}H_{45}N_5O_5$ 675; found 676 (M + H, 85).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(1-propylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8f). The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(1-propylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-*2*-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 0.87 (t, 7 Hz, 3H), 1.44 (dd; 16, 8 Hz; 2H), 1.53 (s, 3H), 1.62 (s, 3H), 2.25 (m, 2H), 2.58 (m, 2H), 3.08 (t, 7 Hz, 2H), 4.14 (s, 2H), 4.37 (dd; 12, 9 Hz; 1H), 4.97 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.10−7.41 (m, 12H). FAB-MS: calculated for $C_{32}H_{39}N_5O_3$ 541; found 542 (M + H, 100).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(1-methylethyl)amino]carbonyl]-amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8 g). 2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[[(1-methylethyl)amino]carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide. The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide, trifluoroacetate and isopropyl isocyanate according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.06 (d, 6.5 Hz, 6H), 1.39 (s, 6H), 1.82 (m, 1H), 2.19−2.58 (m, 3H), 3.74 (m, 1H), 4.12 (s, 2H), 4.32 (m, 1H), 4.87 (d, 15 Hz, 1H), 5.01 (s, 2H), 5.31 (d, 15 Hz, 1H), 7.08−7.40 (m, 17H). FAB-MS: calculated for $C_{40}H_{45}N_5O_5$ 675; found 676 (M + H, 80).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(1-methylethyl)amino]carbonyl]amino]methyl][1,1′-biphenyl]-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8g). The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[[(1-methylethyl)amino]carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.06 (d, 6.5 Hz, 6H), 1.53 (s, 3H), 1.62 (s, 3H), 2.25 (m, 2H), 2.58 (m, 2H), 3.74 (m, 1H), 4.14 (s, 2H), 4.37 (dd; 12, 8 Hz; 1H), 4.97 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.10−7.41 (m, 12H). FAB-MS: calculated for $C_{32}H_{39}N_5O_3$ 541; found 542 (M + H, 100).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(cyclopropylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8h). 2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(cyclopropylamino)-carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide. Prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide, hydrochloride and cyclopropyl isocyanate (prepared in situ from cyclopropylamine and carbonyl-1,1′-diimidazole according to the procedure described in for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 0.39 (m, 2H), 0.61 (m, 2H), 1.38 (s, 6H), 1.82 (m, 1H), 2.18−2.58 (m, 4H), 4.18 (s, 2H), 4.32 (m, 1H), 4.86 (d, 15 Hz, 1H), 5.00 (s, 2H), 5.21 (d, 15 Hz, 1H), 7.10 (m, 1H), 7.14−7.40 (m, 16H). FAB-MS: calculated for $C_{40}H_{43}N_5O_5$ 673; found 674 (M + H, 70).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(cyclopropylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(R)-yl]propanamide, Trifluoroacetate (8h). The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(cyclopropylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-*2*-oxo-1*H*-benzazepin-3(*R*)-yl]propana-

mide according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 0.39 (m, 2H), 0.62 (m, 2H), 1.53 (s, 3H), 1.62 (s, 3H), 2.10−2.45 (m, 3H), 2.58 (m, 2H), 4.19 (s, 2H), 4.37 (m, 1H), 4.98 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.08−7.40 (m, 12H). FAB-MS: calculated for $C_{32}H_{37}N_5O_3$ 539; found 540 (M + H, 80).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(*N*,*N*-dimethylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8i). 2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(*N*,*N*-dimethylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide. Prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide, hydrochloride and dimethylcarbamyl chloride according to the procedure described for **8b**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.39 (s, 6H), 1.82 (m, 1H), 2.18−2.58 (m, 3H), 2.81 (s, 6H), 4.20 (d, 5 Hz, 2H), 4.32 (m, 1H), 4.86 (d, 15 Hz, 1H), 5.01 (s, 2H), 5.31 (d, 15 Hz, 1H), 6.40 (t, 5 Hz, 1H), 7.06−7.40 (m, 17H). FAB-MS: calculated for $C_{39}H_{43}N_5O_5$ 661; found 662 (M + H, 80).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(*N*,*N*-dimethylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8i). The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(*N*,*N*-dimethylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.53 (s, 3H), 1.62 (s, 3H), 2.25 (m, 2H), 2.58 (m, 2H), 2.83 (s, 6H), 4.22 (s, 2H), 4.38 (dd; 11, 9 Hz; 1H), 4.98 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.10 (m, 1H), 7.17−7.37 (m, 11H). FAB-MS: calculated for $C_{31}H_{37}N_5O_3$ 527; found 528 (M + H, 100).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(benzylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]-methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8j). 2-Benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(benzylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide. The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-(aminomethyl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]propanamide, trifluoroacetate and benzyl isocyanate according to the procedure for **8e**. FAB-MS: calculated for $C_{44}H_{45}N_5O_5$ 723; found 724 (M + H, 100). ^{1}H NMR (200 MHz, CD_3OD): δ 1.38 (s, 6H), 1.82 (m, 1H), 2.15−2.55 (m, 3H), 4.14 (s, 2H), 4.24 (s, 2H), 4.32 (m, 1H), 4.85 (d, 15 Hz, 1H), 5.00 (s, 2H), 5.32 (d, 15 Hz, 1H), 7.05−7.42 (m, 22H).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(benzylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]-methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (8j). The title compound was prepared from 2-benzyloxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(benzylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide according to the procedure for **8e**. FAB-MS: calculated for $C_{36}H_{39}N_5O_3$ 589; found 590 (M + H, 80). ^{1}H NMR (200 MHz, CD_3OD): δ 1.53 (s, 3H), 1.62 (s, 3H), 2.25 (m, 2H), 2.58 (m, 2H), 4.17 (s, 2H), 4.26 (s, 2H), 4.37 (dd, 11, 8 Hz; 1H), 4.96 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.10−7.41 (m, 17H).

3-Amino-3-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(methylamino)-carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]-methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]butanamide, Trifluoroacetate (8a). 2,2-Dimethylbutanedioic Acid, 4-Methyl Ester. 2,2-Dimethylsuccinic acid (20 g, 140 mmol) dissolved in 200 mL of absolute methanol at 0° was treated dropwise with 2 mL of concentrated sulfuric acid. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 16 h.

The mixture was concentrated under vacuum to 50 mL and slowly treated with 200 mL of saturated aqueous sodium bicarbonate. The mixture was washed with hexane (3×) and the aqueous layer removed and cooled in an ice bath. The mixture was acidified to pH 2 by slow addition of 6 N HCl and then extracted with ether (8×). The combined extracts were washed with brine, dried over magnesium sulfate, and filtered and solvents removed under vacuum. The residue was dried at room temperature under vacuum to afford 14.7 g (91.8 mmol, 67%) of a viscous oil that slowly solidified upon standing. ^{1}H NMR analysis indicates the product is a mixture of the desired compound and 15% of the isomeric 2,2-dimethylbutanedioic acid, 1-methyl ester. NMR (200 MHz, $CDCl_3$) of desired compound: δ 1.29 (s, 6H), 2.60 (s, 2H), 3.66 (s, 3H). NMR (200 MHz, $CDCl_3$) isomer: d 1.28 (s, 6H), 2.63 (s, 2H), 3.68 (s, 3H).

3-[Benzyloxycarbonylamino]-3-methylbutanoic Acid, Methyl Ester. To 14.7 g (91.8 mmol) of 2,2-dimethylbutanedioic acid 4-methyl ester, containing 15% of the isomeric 1-methyl ester compound, in 150 mL of benzene was added 13 mL of triethylamine (9.4 g, 93 mmol, 1.01 equiv) followed by 21.8 mL of diphenylphosphoryl azide (27.8 g, 101 mmol, 1.1 equiv). The mixture was heated under nitrogen at reflux for 45 min then 19 mL (19.9 g, 184 mmol, 2 equiv) of benzyl alcohol was added and refluxing continued for 16 h.

The mixture was cooled and filtered and the filtrate concentrated to a minimum volume under vacuum. The residue was redissolved in 250 mL of ethyl acetate and washed with water, saturated aqueous sodium bicarbonate (2×), and brine. The organic layer was removed, dried over magnesium sulfate, and filtered and the filtrate concentrated to a minimum volume under vacuum. The crude product was purified by medium-pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (4:1), to afford 18.3 g (68.9 mmol, 75%) of the product as a pale yellow liquid in addition to a small amount of pure 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester. ^{1}H NMR (200 MHz, $CDCl_3$) of major product: δ 1.40 (s, 6H), 2.69 (s, 2H), 3.63 (s, 3H), 5.05 (s, 2H), 5.22 (br s, 1H), 7.32 (s, 5H). ^{1}H NMR (200 MHz, $CDCl_3$) of 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester (200 MHz, $CDCl_3$): δ 1.19 (s, 6H), 3.30 (d, 7 Hz, 2H; resonance collapses to singlet in CD_3OD), 3.67 (s, 3H), 5.09 (s, 2H), 5.22 (br s; 1H; resonance absent in CD_3OD), 7.3 (br s, 5H).

3-Benzyloxycarbonylamino-3-methylbutanoic Acid (5c). A solution of 18.3 g (68.9 mmol) of methyl 3-benzyloxycarbonylamino-3-methylbutanoate in 20 mL of methanol at room temperature was treated dropwise with 51 mL of 2 N NaOH (102 mmol, 1.5 equiv). The mixture was stirred at room temperature for 16 h, transferred to a separatory funnel, and washed with hexane (3×). The aqueous layer was removed, cooled to 0 °C, and slowly acidified to pH 2 (paper) by dropwise addition of 6 N HCl. This mixture was extracted with ether (6×); combined extracts were washed with 1 N HCl and brine, then over magnesium sulfate, and filtered, and solvent was removed under vacuum to afford 17.3 g (68.7 mmol, 99%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 6H), 2.77 (s, 2H), 5.06 (s, 2H), 5.2 (br s, 1H), 7.3 (s, 5H).

3-Benzyloxycarbonylamino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3(*R*)-yl]butanamide (4c). Prepared from 3-benzyloxycarbonylamino-3-methylbutanoic acid (**4c**) and 3(*R*)-amino-2,3,4,5-tetrahydro-1*H*-benzazepin-2-one (**3**) substituting benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate for benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate according to the procedure described for **5a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 6H), 1.82 (m, 1H), 2.45−2.75 (m, 4H), 2.86 (m, 1H), 4.49 (m, 1H), 5.05 (dd; 10, 6 Hz; 2H), 5.55 (s, 1H), 6.73 (s, 1H), 6.96 (d, 4 Hz, 1H), 7.10−7.40 (m, 8H), 8.68 (s, 1H). FAB-MS: calculated for $C_{23}H_{27}N_3O_4$ 409; found 410 (M + H, 100).

2′-[(*tert*-Butoxycarbonylamino)methyl]-1,1′-biphenyl-4-methanol, Acetate Ester. To solution of 500 mg (1.60 mmol) of 2′-[(*tert*-butoxycarbonylamino)methyl]-1,1′-biphenyl-4-methanol in 1 mL of dry methylene chloride under a nitrogen

atmosphere at room temperature was added by syringe 0.267 mL (1.91 mmol) of triethylamine followed by 0.165 mL (1.76 mmol) of acetic anhydride. The reaction mixture was stirred for 1 h, diluted with 150 mL of ethyl acetate, washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried over magnesium sulfate, and filtered. The solvent was removed under vacuum to give 583 mg (>100%, containing a minor amount of ethyl acetate) of the product as a white solid which was used in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.10 (s, 3H), 4.22 (d, 6 Hz, 2H), 4.65 (s, 1H), 5.12 (s, 2H), 7.18−7.48 (m, 8H). FAB-MS: calculated for $C_{21}H_{25}NO_4$ 355; found 356 (M + H).

2′-Aminomethyl-1,1′-biphenyl-4-methanol, Acetate Ester, Trifluoroacetate. Prepared from 2′-[(*tert*-butoxycarbonylamino)methyl]-1,1′-biphenyl-4-methanol, acetate ester according to the procedure described for **8e**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.03 (s, 3H), 3.98 (s, 2H), 5.07 (s, 2H), 7.18−7.48 (m, 8H), 7.75 (s, 3H). FAB-MS: calculated for $C_{16}H_{17}NO_2$ 255; found 256 (M + H, 80).

2′-[[(Methylamino)carbonyl]amino]methyl-1,1′-biphenyl-4-methanol, Acetate Ester. Prepared from 2′-aminomethyl-1,1′-biphenyl-4-methanol, acetate ester, trifluoroacetate according to the procedure described for **8e**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.65 (d, 4.8 Hz, 3H), 4.27 (d, 4.8 Hz, 2H), 4.52 (m, 1H), 5.12 (s, 2H), 7.18−7.48 (m, 8H). FAB-MS: calculated for $C_{18}H_{20}N_2O_3$ 312; found 313 (M + H, 100).

2′-[[(Methylamino)carbonyl]amino]methyl-1,1′-biphenyl-4-methanol. To a solution of 498 mg (1.60 mmol) of 2′-[[(methylamino)carbonyl]amino]methyl-1,1′-biphenyl-4-methanol, acetate ester in 10 mL of THF/water (3:1) was added 335 mg (7.98 mmol) of lithium hydroxide monohydrate. After 16 h of stirring at room temperature, the reaction mixture was diluted with 150 mL of ethyl acetate and washed with brine (3 × 50 mL). The organic layer was dried over magnesium sulfate and filtered and the solvent removed under vacuum to afford 411 mg (95%) of the product as a white solid. ^{1}H NMR (200 MHz, CD_3OD): δ 2.64 (s, 3H), 4.20 (s, 2H), 4.62 (s, 2H), 7.12−7.45 (m, 8H). FAB-MS: calculated for $C_{16}H_{18}N_2O_2$ 270; found 271 (M + H, 100).

2′-[[(Methylamino)carbonyl]amino]methyl-1,1′-biphenyl-4-methanol, Methanesulfonate Ester (6c). To solution of 100 mg (0.17 mmol) of 2′-[[(methylamino)carbonyl]amino]-methyl-1,1′-biphenyl-4-methanol (step H) in 5 mL of dry methylene chloride and 1 mL dry dimethylformamide under a nitrogen atmosphere at 0 °C was added by syringe 0.077 mL (0.56 mmol) of triethylamine followed by 0.034 mL (0.44 mmol) of methanesulfonyl chloride. The reaction mixture was stirred for 30 min at 0 °C, diluted with 75 mL of methylene chloride, washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried over sodium sulfate, and filtered. The solvent was removed under vacuum to give 128 mg (100%) of the product as a white solid which was used in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.66 (d, 4 Hz, 3H), 2.97 (s, 3H), 4.26 (d, 5 Hz, 2H), 4.42 (m, 1H), 5.26 (s, 2H), 7.18−7.48 (m, 8H). FAB-MS: calculated for $C_{17}H_{20}N_2O_4S$ 348; found 349 (M + H, 100).

3-Benzyloxycarbonylamino-3-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(methyl-amino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]butanamide. Prepared from 3-benzyloxycarbonylamino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3(*R*)-yl]-butanamide (**5c**) and 2′-[[(methylamino)carbonyl]amino]-methyl-1,1′-biphenyl-4-methanol, methanesulfonate ester (**6c**) according to the procedure described for **8b**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 6H), 1.78 (m, 1H), 2.37−2.63 (m, 3H), 2.60 (d, 5 Hz, 3H), 4.20 (d, 6 Hz, 2H), 4.52 (m, 2H), 4.72 (t, 6 Hz, 1H), 4.86 (d, 16 Hz, 1H), 4.89 (s, 2H), 5.10 (d, 15 Hz, 1H), 5.69 (s, 1H), 6.73 (d, 7.5 Hz, 1H), 7.08−7.35 (m, 16H) 7.40 (m, 1H). FAB-MS: calculated for $C_{39}H_{43}N_5O_5$ 661; found 662 (M + H, 40).

3-Amino-3-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(methyl-amino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]-methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]butanamide, Trifluoroacetate (8a). The title compound was prepared from 3-benzyloxycarbonylamino-3-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[[[(methylamino)carbonyl]amino]methyl][1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]butanamide according to the procedure described for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.32 (s, 3H), 1.35 (s, 3H), 2.0−2.35 (m, 2H), 2.40−2.62 (m, 4H), 2.65 (s, 3H), 4.14 (dd; 17, 15 Hz; 2H), 4.40 (dd; 12, 8 Hz; 1H), 4.97 (d, 15 Hz, 1H), 5.21 (d, 15 Hz, 1H), 7.10−7.41 (m, 12H). FAB-MS: calculated for $C_{31}H_{37}N_5O_3$ 527; found 528 (M + H, 100).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[2-[[methylaminocarbonyl]amino]ethyl][1,1′-biphenyl]-4-yl]-methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (10). 2-*tert*-Butoxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3(*R*)-yl]-propanamide (5d). Prepared from *N*-*tert*-butoxycarbonyl-2-methylalanine (**4d**) and 3(*R*)-amino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**3**) substituting benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate for benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate according to the procedure for **5a**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 3H), 1.52 (s, 3H), 1.82 (m, 1H), 2.50−3.00 (m, 3H), 4.45 (m, 1H), 5.05 (s, 2H), 5.37 (s, 1H), 6.80−7.40 (m, 10H), 8.65 (s, 1H). FAB-MS: calculated for $C_{22}H_{25}N_3O_4$ 395; found 396 (M + H, 100).

2′-(Cyanomethyl)-1,1′-biphenyl-4-methanol, *tert*-Butyldiphenylsilyl Ether. To a solution of 1.50 g (3.84 mmol) of 4-(*tert*-butyldiphenylsilyoxymethyl)phenylboronic acid in 8 mL of dry dimethylformamide was added 220 mg (0.19 mmol) of tetrakis(triphenylphosphine) palladium, 1.2 g (5.8 mmol) of tripotassium phosphate and 0.791 g (4.03 mmol) of 2-bromophenylacetonitrile. The resulting mixture was heated under nitrogen at 100 °C for 3 h and then cooled to room temperature. The reaction mixture was diluted with 100 mL of saturated aqueous ammonium chloride, transferred to a separatory funnel, and extracted with ether (3 × 150 mL). The combined ether extracts were washed with saturated aqueous sodium bicarbonate (100 mL) and saturated aqueous sodium chloride (100 mL), dried over magnesium sulfate, and filtered. The solvent was removed under vacuum to give a crude product which was purified by flash column chromatography on silica gel eluting with hexanes/ethyl acetate (9:1) to afford 1.3 g (73%) of the product as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 9H), 3.82 (s, 2H), 4.82 (s, 2H), 7.18−7.47 (m, 11H), 7.50−7.62 (m, 3H), 7.73 (m, 4H). FAB-MS: calculated for $C_{31}H_{31}NOSi$ 461; found 462 (M + H, 20).

2′-(Cyanomethyl)-1,1′-biphenyl-4-methanol. Prepared from 2′-(cyanomethyl)-1,1′-biphenyl-4-methanol, *tert*-butyldiphenylsilyl ether according to the procedure described for **6b**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.93 (s, 1H), 3.60 (s, 2H), 4.73 (d, 4 Hz, 2H), 7.27 (m, 3H), 7.33−7.63 (m, 5H). FAB-MS: calculated for $C_{15}H_{13}NO$ 223; found 222 (M − H), 205 (M − H_2O, 100).

2′-(Cyanomethyl)-1,1′-biphenyl-4-methanol, *tert*-butyldimethylsilyl Ether. To a solution of 145 mg (0.65 mmol) of 2′-(cyanomethyl)-1,1′-biphenyl-4-methanol in 2 mL of dry dimethylformamide under a nitrogen atmosphere was added 66 mg (0.97 mmol) of imidazole. The reaction mixture was cooled to 0 °C, and 117 mg (0.78 mmol) of *tert*-butyldimethylsilyl chloride was added. The resulting solution was stirrred at 0 °C for 15 min and then at room temperature for 16 h. The reaction mixture was poured into 100 mL of water and extracted with ether (3 × 35 mL). The combined ether extracts were washed with water (25 mL), saturated aqueous sodium bicarbonate (25 mL), and brine (25 mL). The organic layer was dried over magnesium sulfate and filtered and the solvent removed under vacuum to give 222 mg (100%) of an oil which used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.94 (s, 9H), 3.60 (s, 2H), 4.77 (s, 2H), 7.24 (m, 3H), 7.40 (m, 4H), 7.52 (m, 1H). FAB-MS: calculated for $C_{21}H_{27}$-NOSi 337; found 336 (M − H, 10), 206 (100).

2′-(2-Aminoethyl)-1,1′-biphenyl-4-methanol. To a solution of 219 mg (0.65 mmol) of 2′-(2-cyanomethyl)-1,1′-biphenyl-4-methanol, *tert*-butyldimethylsilyl ether in 6 mL of dry methylene chloride under a nitrogen atmosphere was added 501 mg (1.95 mmol) of tetra-*n*-butylammonium borohydride. The reaction mixture was heated at reflux for 9 h and cooled to room temperature and the solvent removed under vacuum to give an oil which was dissolved in 2 mL of tetrahydrofuran and treated with 2 mL of 10% aqueous hydrochloric acid. The resulting solution was heated at reflux for 1 h, cooled in an ice bath, and treated with 5 N aqueous sodium hydroxide until pH = 12. The mixture was extracted with ethyl acetate (3 × 35 mL). The organic extracts were washed with water (25 mL), saturated aqueous sodium bicarbonate (25 mL), and brine (25 mL). The organic layer was dried over sodium sulfate and filtered and the solvent removed under vacuum to give an oil which was purified by flash column chromatography on silica gel, eluting with chloroform/10% ammonium hydroxide (33%) in methanol (9:1) to afford 129 mg (87%) of the product as an off-white solid. ^{1}H NMR (200 MHz, CD_3OD): δ 2.63 (m, 2H), 2.75 (m, 2H), 4.63 (s, 2H), 7.10−7.32 (m, 6H), 7.39 (d, 8 Hz, 2H). FAB-MS: calculated for $C_{15}H_{17}NO$ 227; found 242 (M + 2Li, 100).

2′-[2-[Methylaminocarbonyl]amino]ethyl-1,1′-biphenyl-4-methanol. Prepared from 2′-(2-aminoethyl)-1,1′-biphenyl-4-methanol according to the procedure described for **6c**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.56 (d, 5 Hz, 3H), 2.70 (t, 8 Hz, 2H), 2.89 (t, 5 Hz, 1H), 3.10 (m, 2H), 4.37 (m, 1H), 4.52 (t, 6 Hz, 1H), 4.67 (d, 5 Hz, 2H), 7.12−7.30 (m, 6H), 7.35 (d, 8 Hz, 1H). FAB-MS: calculated for $C_{17}H_{20}N_2O_2$ 284; found 285 (M + H, 100).

2′-[2-[Methylaminocarbonyl]amino]ethyl-1,1′-biphenyl-4-methanol, Methanesulfonate Ester (6d). Prepared from 2′-[2-[methylaminocarbonyl]amino]ethyl-1,1′-biphenyl-4-methanol and methanesulfonyl chloride according to the procedure described for **6c** and used in the next step without purification.

2-*tert*-Butoxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[2-[[methylaminocarbonyl]amino]ethyl]-[1,1′-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide. Prepared from 2-*tert*-butoxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide (**5d**) and 2′-[2-[methylaminocarbonyl]amino]-ethyl-1,1′-biphenyl-4-methanol, methanesulfonate ester (**6d**) according to the procedure described in for **8b**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (s, 12H), 1.41 (s, 3H), 1.85 (m, 1H), 2.40−2.80 (m, 8H), 3.13 (m, 2H), 4.25 (m, 2H), 4.47 (m, 1H), 4.94 (d, 16 Hz, 1H), 4.96 (s, 1H), 5.11 (d, 16 Hz, 1H), 7.08−7.20 (m, 12H). FAB-MS: calculated for $C_{36}H_{45}N_5O_5$ 627; found 628 (M + H, 20), 528 (100).

2-Amino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[2-[[methylaminocarbonyl]amino]ethyl][1,1′-biphenyl]-4-yl]-methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide, Trifluoroacetate (10). The title compound was prepared from 2-*tert*-butoxycarbonylamino-2-methyl-*N*-[2,3,4,5-tetrahydro-1-[[2′-[2-[[methylaminocarbonyl]amino]ethyl][1,1′-biphenyl]-4-yl]-methyl]-2-oxo-1*H*-benzazepin-3(*R*)-yl]propanamide according to the procedure described for **8b**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.53 (s, 3H), 1.62 (s, 3H), 2.25 (m, 2H), 2.59 (m, 5H), 2.67 (t, 7 Hz, 2H), 4.37 (dd; 12, 9 Hz; 1H), 4.96 (d, 15 Hz,1H), 5.21 (d, 15 Hz, 1H), 7.08−7.38 (m, 12H). FAB-MS: calculated for $C_{31}H_{37}N_5O_3$ 527; found 528 (M + H, 100).

3-Amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-aminomethyl-[1,1′-biphenyl]-4yl]methyl]-1*H*-benzazepin-3(*R*)-yl]butanamide, Ditrifluoroacetate (9b). 3-(Benzyloxycarbonyl)amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[(*tert*-butoxycarbonylamino)methyl][1,1′-biphenyl]-4yl]methyl]-1H-benzazepin-3(*R*)-yl]butanamide. The title compound was prepared from 3-(benzyloxycarbonyl)amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepin-3(*R*)-yl]butanamide (**5c**) and 2′-[(*tert*-butoxycarbonylamino)methyl]-1,1-biphenyl-4-methanol methanesulfonate ester (**6b**) according to the procedure for **8b**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.32 (s, 3H), 1.37 (s, 9H), 1.76 (m, 1H), 2.30−2.62 (m, 5H), 4.15 (d, 5 Hz, 2H), 4.40−4.60 (m, 2H), 4.85 (d, 14 Hz, 1H), 4.95 (d, 10 Hz, 1H), 5.04 (d, 10 Hz, 1H), 5.18 (d, 14 Hz, 1H), 5.65 (s, 1H), 6.70 (d, 6 Hz, 1H), 7.10−7.42 (m, 17H). FAB-MS: calculated for $C_{42}H_{48}N_4O_6$ 704; found 705 (M + 1, 40).

3-(Benzyloxycarbonyl)amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-aminomethyl-[1,1′-biphenyl]-4yl]-methyl]-1H-benzazepin-3(*R*)-yl]butanamide, Trifluoroacetate. The title compound was prepared from 3-(benzyloxycarbonyl)amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[(*tert*-butoxycarbonylamino)methyl][1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]butanamide according to the procedure for **8e**. ^{1}H NMR (200 MHz, CD_3OD): δ 1.40 (s, 6H), 2.04 (m, 1H), 2.31 (m, 2H), 2.55 (d, 12 Hz, 1H), 2.62 (m, 2H), 4.08 (s, 2H), 4.42 (dd; 12, 8 Hz; 1H), 5.01 (d, 12 Hz, 1H), 5.07 (d, 14 Hz, 1H), 5.10 (d, 12 Hz, 1H), 5.15 (d, 14 Hz, 1H), 7.20−7.60 (m, 17H). FAB-MS: calculated for $C_{37}H_{40}N_4O_4$ 604; found 605 (M + 1, 80).

3-Amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-aminomethyl-[1,1′-biphenyl]-4yl]methyl]-1*H*-benzazepin-3(*R*)-yl]butanamide, Ditrifluoroacetate. The title compound was prepared from 3-(benzyloxycarbonyl)amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-aminomethyl[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]butanamide trifluoroacetate according to the procedure for **8e** ^{1}H NMR (200 MHz, CD_3OD): 1.34 (s, 3H), 1.37 (s, 3H), 2.0−2.70 (m, 6H), 4.02 (s, 2H), 4.40 (dd; 13, 7 Hz; 1H), 4.93 (d; 14 Hz; 1H), 5.22 (d; 14 Hz; 1H), 7.1−7.55 (m, 12H). FAB-MS: calculated for $C_{29}H_{34}N_4O_2$ 470; found 471 (M + H, 90).

3-Amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[acetamidomethyl][1,1′-biphenyl]-4yl]methyl]-1*H*-benzazepin-3(*R*)-yl]butanamide, Trifluoroacetate (9a). 3-(Benzyloxycarbonyl)amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-acetamidomethyl[1,1′-biphenyl]-4yl]methyl]-1*H*-benzazepin-3(*R*)-yl]butanamide. To a solution of 24 mg (0.038 mmol) of 3-(benzyloxycarbonyl)amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-aminomethyl[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]butanamide, trifluoroacetate dissolved in 1 mL of dry methylene chloride was added by syringe 0.011 mL (0.076 mmol) of triethylamine followed by 0.005 mL (0.076 mmol) of acetyl chloride. The resulting mixture was stirred overnight. The reaction mixture was diluted with 75 mL of ethyl acetate, washed with water, saturated sodium bicarbonate, and then brine, dried over magnesium sulfate, and filtered. The solvent was removed under vacuum to give an oil which was purified by by flash column chromatography on silica gel eluting with ethyl acetate/methanol (96:4) to afford 17 mg (71%) of the title compound as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): 1.37 (s, 3H), 1.39 (s, 3H), 1.78 (m, 1H), 1.90 (s, 3H), 2.35−2.62 (m, 5H), 4.31 (d, 5 Hz, 2H), 4.50 (m, 1H), 4.90 (d, 14 Hz, 1H), 4.98 (d, 12 Hz, 1H), 5.05 (d, 12 Hz, 1H), 5.17 (d, 14 Hz, 1H), 5.62 (m, 2H), 6.68 (d, 7 Hz, 1H), 7.10−7.70 (m, 17H). FAB-MS: calculated for $C_{39}H_{42}N_4O_5$ 646; found 647 (M + 1, 60).

3-Amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[acetamidomethyl][1,1′-biphenyl]-4yl]methyl]-1*H*-benzazepin-3(*R*)-yl]butanamide, Trifluoroacetate (9a). To the title compound was prepared from 3-(benzyloxycarbonyl)-amino-3-methyl-*N*-[2,3,4,5-tetrahydro-2-oxo-1-[[2′-[acetamidomethyl[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(*R*)-yl]-butanamide according to the procedure for **8e** ^{1}H NMR (200 MHz, CD_3OD): 1.31 (s, 3H), 1.34 (s, 3H), 1.88 (s, 3H), 2.0−2.68 (m, 6H), 4.20 (s, 2H), 4.40 (dd; 11, 8 Hz; 1H), 4.97 (d, 14 Hz, 1H), 5.24 (d, 14 Hz, 1H), 7.1−7.40 (m, 12H). FAB-MS: calculated for $C_{31}H_{36}N_4O_3$ 512; found 513 (M + H, 100).

Rat Pituitary Cell Assay. Cell Culture. Wistar male rats (150−200 g) were obtained from Charles River Laboratories (Wilmington, MA). Rats were maintained at a constant temperature (25 °C) on a 14-h light, 10-h dark cycle. Rat chow and water were available ad libitum. Animals were sacrificed by decapitation and anterior lobes of the pituitary quickly removed. Rat pituitary cells were isolated from pituitaries by enzymatic digestion with 0.2% collagenase and 0.2% hyaluronidase in Hank's Balanced Salt Solution as described previously.[22] For culture, cells were suspended in culture medium

and adjusted to a final concentration of 1.5×10^5 cells/mL; 1.0 mL of this suspension was placed in each well of a 24-well tray (Costar; Cambridge, MA). Cells were maintained in a humidified 5% CO_2−95% air atmosphere at 37 °C for 3−4 days. The culture medium consisted of Dulbecco's Modified Eagle's Medium containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% fetal bovine serum, 1% nonessential amino acids, 1% glutamine, 1% nystatin, and 0.1% gentamycin.

Experiments for GH Release. On the day of an experiment, cells were washed twice 90 min prior to and once more immediately before the start of the experiment with the above culture medium containing 25 mM HEPES, pH 7.4. Stock solutions of 2 mg/mL of the test agents were prepared in dimethyl sulfoxide, and serial dilutions in the culture medium were made from the stock solutions. The final concentration of DMSO in the assay medium was 1%. GH release was initiated by adding 1 mL of fresh medium containing test agents to each well in quadruplicate. Incubation was carried out at 37 °C for 15 min. After incubation, medium was removed and centrifuged at 2000*g* for 15 min to remove any cellular material. The supernatant fluid was removed and assayed for GH content.

Radioimmunoassays. Rat GH in culture medium was measured by a double antibody RIA procedure using materials obtained from Dr. A. F. Parlow (Harbor-UCLA Medical Center, Torrance, CA) and expressed in terms of the standard rat GH RP-2.

Data Analyses. ED_{50} values for test compounds were computed by fitting a four-parameter logistic function to the dose−response curve.[23] Least squares estimates of the four-parameter logistic function coefficients and their variances were derived using the iterative algorithm described by Bates and Watts.[24]

In Vivo Efficacy in Beagle Dogs. Formulations of the hydrochloride salt of L-739,943 were prepared at 0.10, 0.20, and 0.40 mg/mL in distilled water. All formulations were calcultaed as base compound and were administered at 5 mL/kg of body weight resulting in dosages of 0 (placebo), 0.50, 1.0, and 2.0 mg/kg of L-739,943.

Eight beagle dogs, four male and four female, 3 years of age and 10−16 kg in weight were used. The four dosages were allocated to the eight dogs in a crossover design. There was a 7 day interval between each treatment in each dog. Dogs were fasted for 15 h prior to and during treatment. Treatments were administered via stomach tube in a volume of water equal to 5 mL/kg of body weight. Dogs were bled from the jugular vein at −0.33, 0 (before dosing), 0.33, 0.66, 1.0, 1.5, 2.0, 3.0, 4.0, and 6 h after dosing. From the blood collected at each sampling, the sera were separated and asayed for GH and other hormones by RIA.

Bioavailability in Beagle Dogs. In a two period crossover study, beagle dogs (11.5−16.5 kg body weight) were dosed orally by gavage with L-739,943 (HCl or TFA salt) at 1.6 mg/kg or intravenously at 0.16 mg/kg by bolus injection into the cephalic vein by an indwelling catheter (22 gauge) at 0.16 mg/kg (all doses calculated as base compound). There was a 7 day interval between each treatment in each dog. Dogs were bled from the jugular vein into a heparin containing Vacutainer tube at 2.5 min (iv only), 5, 15, and 30 min., and at 1, 2, 4, 6,8, 24, 48, and 72 h after dosing. From the blood collected at each sampling, plasma was obtained by centrifugation at 2000*g* for 10 min and stored at −20 °C until analyzed by LC/MS/MS versus an internal standard.

Concentrations of L-739,943 in plasma were determined using LC/MS/MS assay following solid-phase extraction (SPE) on a BondElut Certify cartridge (Varian). An aliquot of plasma was mixed with 20 ng of an internal standard and acidified with an equal volume of 1% phosphoric acid. The resulting mixture was applied to the SPE cartridge which had been preconditioned with 2.5 mL of methanol followed by 2 mL of water and 2 mL of 0.1 M phosphate buffer, pH 2.5. After washing with 2 mL of water, the cartridge was eluted with methanol containing 5% ammonium hydroxide. The methanol extract was dried under nitrogen at room temperature and the residue was reconstituted in 100 μL of acetonitrile/water (90:10) and an aliquot of 1−20 μL was analyzed by LC/MS/MS.

The HPLC system consisted of two Shimadzu LC-600 pumps. an SCL-6B controller, and an SIL-6B autoinjector. Chromatography was carried out at on a Spheresorb C8 (5 μm, 4.6 × 50 mm) column using isocratic mobile phase consisting of either (A) 47% acetonitrile/23% methanol/10% 5 mM ammonium acetate/0.1% formic acid or (B) 90% acetonitrile/30% 5 mM ammonium acetate/0.1% formic acid. The flow rate was 1.0 mL/min.

LC/MS/MS assays were performed on a SCIEX API II tandem mass spectrometer using the heated nebulizer interface. Mass spectra and production spectra were obtained using an ionspray interface and positive ion detection was used with argon as the collision gas. The column effluent was split (splitter ratio 1:25) such that 4% entered the ion spray interface.

Areas under the plasma concentration versus time curve (AUC) were determined by the UNICUE program with linear trapezoidal interpolation in the ascending slope and logarithmic trapezoidal interpolation in the descending slope.[25] The concentration of L-739,943 at t_o after intravenous dosing was estimated by the Levenberg/Marquardt nonlinear optimization algorithm using the RSTRIP Program (MicroMath Scientific Software). The portion of the AUC from the last measurable plasma concentration to infinity was estimated by C_t/λ where C_t represents the last measurable plasma concentration and λ is the terminal rate constant determined from the plasma concentration versus time curve by the linear regression of the elimination phase of the semilogarithmic plot. The portion of the AUMC from the last measurable plasma concentration to infinity was estimated by $tC_t/\lambda + C_t/\lambda^2$. The volume of distribution at steady state (Vd_{ss}), elimination half-life ($t_{1/2}$), plasma clearance (Cl_p), and oral bioavailability (F) were calculated by the following equations:

$$Vd_{ss} = \text{dose} \times AUMC_{(0-\infty)}/AUC_{(0-\infty)}^{\ 2}$$

$$t_{1/2} = 0.693/\lambda$$

$$Cl_p = \text{dose}/AUC_{(0-\infty)}$$

$$F\ (\%) = AUC_{(po)} \times \text{dose}_{(iv)}/AUC_{(iv)} \times \text{dose}_{(po)}$$

The dose was converted to mg of free base/kg in the calculation of Cl_p and Vd_{ss}. Concentrations lower than the limit of quantification were treated as zero for the purpose of calculation of means.

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