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# Benzolactam Growth Hormone Secretagogues: Carboxamides as Replacements for the 2'-Tetrazole Moiety of L-692,429

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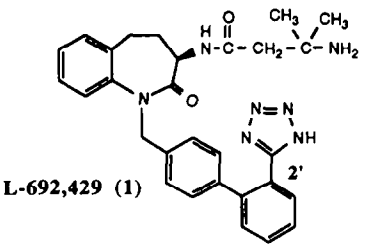
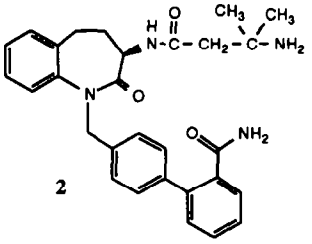
**Abstract:** A variety of 2'-carboxamides was investigated as replacements for the 2'-tetrazole moiety of L-692,429. Investigation of the structure-activity relationships of the carboxamide series determined that primary and secondary carboxamides are potent growth hormone secretagogues *in vitro*. L-700,653 (**11**) was identified as an orally active GH secretagogue in dogs.

The benzolactam class of growth hormone secretagogues represents a novel approach for the non-peptidyl regulation of growth hormone (GH) release in humans. In a previous communication,[1a] we presented the structure-activity relationships of the 2'-position of the biphenyl moiety of L-692,429 (**1**). The 2'-carboxamide analog **2** was identified as a neutral replacement for the tetrazole in this class of GH secretagogues. In this Letter, we report the structure-activity relationships of the carboxamide class of benzolactam GH secretagogues and provide *in vivo* data for L-700,653 (**11**), an orally active carboxamide derivative.




L-692,429 (1)

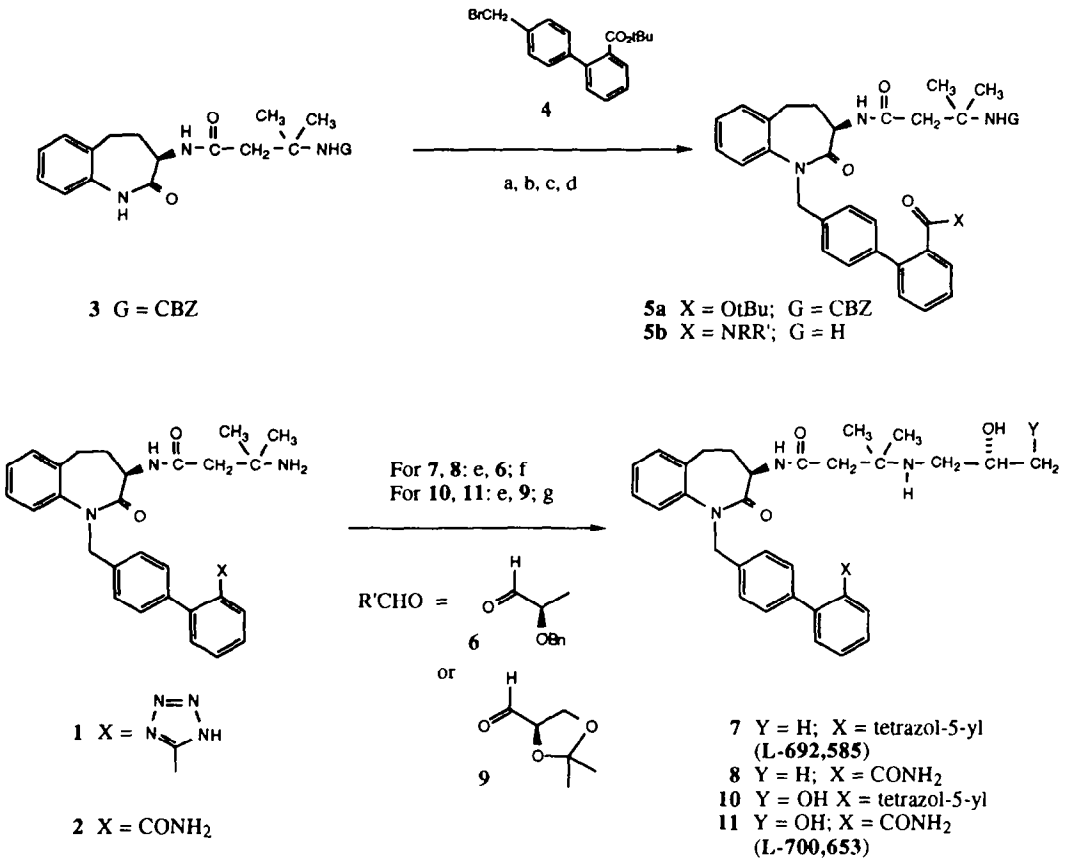



2

**Synthesis:** Preparation of the benzolactam growth hormone secretagogues **1** and **2** has been previously described.[1a,b] The 2'-carboxamide analogs were prepared from the benzolactam intermediate **3** containing the CBZ-protected dimethyl β-alanine sidechain[1b] by deprotonation of the benzolactam nitrogen with sodium hydride in anhydrous dimethylformamide followed by addition of the known 2'-t-butyl ester **4**[1b] to give the methylbiphenyl-2-ester intermediate **5a** in high yield (Scheme I).[2] *N*-Substituted carboxamide analogs **5b** are prepared from the ester intermediate **5a** by cleavage of the t-butyl group with trifluoroacetic acid (TFA) followed by activation of the resulting carboxylic acid with benzotriazol-1-yloxy*tris*(dimethylamino)phosphonium

hexafluorophosphate (BOP or pyBOP) and addition of an amine. Hydrogenolysis of the CBZ-group from the resulting carboxamide affords the *N*-substituted analogs **5b** in high overall yield (approximately 65% for 4 steps).

**SCHEME I**




Reagents and conditions: (a) NaH, DMF, RT, 1 hr (b) TFA, anisole, $CH_2Cl_2$ (c) pyBOP or BOP, TEA, RR'NH, $CH_2Cl_2$ (d) $H_2/Pd(OH)_2$, MeOH, 1hr (e) $NaCNBH_3$, R'CHO, 4Å mol. sieves, pH = 6, 24 hr (f) $H_2$/ Pd-C, 40 psi, TFA, MeOH, 24hr (g) TFA, MeOH, 4 hr.

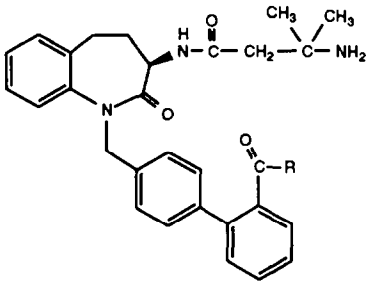
The hydroxyalkyl analogs (e.g., **7**) were prepared by reductive amination of the sidechain amine with an appropriately protected aldehyde. L-692,429 (**1**) or carboxamide **2** was reductively aminated with (R)-2-benzyloxypropionaldehyde **6**[3] and sodium cyanoborohydride followed by hydrogenolysis of the O-benzyl group to give the 2-hydroxypropylamine analogs, tetrazole **7**[4] and carboxamide **8**, respectively. Similarly, reductive amination with D-glyceraldehyde acetonide **9**[5] followed by acidic hydrolysis of the acetonide gave the dihydroxypropyl amine analogs, tetrazole **10** and carboxamide **11**. No racemization was observed at the

hydroxyl stereocenter in the products isolated as determined by HPLC and $^1$H NMR. Other derivatives with differing substitution were prepared by an analogous route from the appropriate starting materials.

**Results and Discussion**

Growth hormone release *in vitro* was measured in rat pituitary cells as previously described.[1b,6] Table 1 displays the key structure-activity relationships of the *N*-substituted carboxamide series of growth hormone secretagogues. Small substituents (e.g., *N*-ethyl **12**) are not detrimental to GH releasing activity while larger substituents (e.g., *N*-benzyl **13**) result in a significant decrease in activity. This can be partially overcome by an appropriate 4-phenyl substituent (cf. **14** vs. **15**). *N,N*-Disubstitution is not tolerated as illustrated with diethylamide **16**, resulting in a 25-fold loss in potency relative to carboxamide **2**. The reduced GH releasing activity for compound **16** underscores the necessity of the carboxamide N-H, although steric/conformational factors cannot be excluded by the available data. The 2-hydroxyethylamide **17** is much less potent than the simple *N*-alkyl substituted amides (e.g., **12**). This may be due to simple internal hydrogen bonding of the hydroxyl group to the carboxamide resulting in an unfavorable conformational change or possibly due to a detrimental ligand-receptor interaction.

**Table 1**



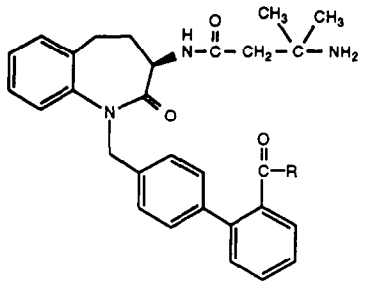
| Compound | R | $ED_{50}$ (μM)[a,b] |
|---|---|---|
| **2** | $NH_2$ | **0.08** |
| **12** | $NHCH_2CH_3$ | **0.09** |
| **13** | $NHCH_2Ph$ | **0.9** |
| **14** | $NHCH_2$(4-Ph-OMe) | **2** |
| **15** | $NHCH_2$(4-Ph-OH) | **0.3** |
| **16** | $N(CH_2CH_3)_2$ | **2** |
| **17** | $NHCH_2CH_2OH$ | **3** |

[a] Rat pituitary cell assay. [b] $ED_{50}$ L-692,429 = 0.06μM

The interesting changes in potency observed with the 4-hydroxybenzyl analog **15** and 2-hydroxyethyl analog **17** as well as the *N*-(2-hydroxypropyl)tetrazole analogs[1a] were explored further by the series of ω-hydroxyalkyl carboxamides shown in Table 2. The *N*-3-hydroxypropyl analog **18** showed a 7.5 fold gain in activity relative to the hydroxyethyl analog **17**. However, further homologation to the *N*-4-hydroxybutyl analog **19** or the 5-hydroxypentyl analog **20** results in an 8-fold increase in potency relative to that of the parent carboxamide **2** and a 300-fold increase in potency relative to that of the 2-hydroxyethyl carboxamide **17**. The data presented suggest that the increasing chain length decreases the ability of the terminal hydroxyl group to form an internal hydrogen bond with the amide functionality. This may result in a more favorable conformation of the carboxamide pharmacophore and a return of GH releasing potency. However, the large increase in potency (>100 fold) observed for analogs containing the 4-hydroxybutyl or 5-hydroxypentyl group (cf. **19**, **20** vs. **21**)

and the 8-fold increase in potency observed over the primary carboxamide (cf. **2** vs. **19**, **20**) illustrates the importance of the terminal hydroxyl group, since its absence leads to a large decrease in potency. The terminal hydroxyl group *may* also be involved in a favorable interaction with the receptor as opposed to *only* modulating the internal hydrogen bonding, conformational or steric parameters of the carboxamide pharmacophore.

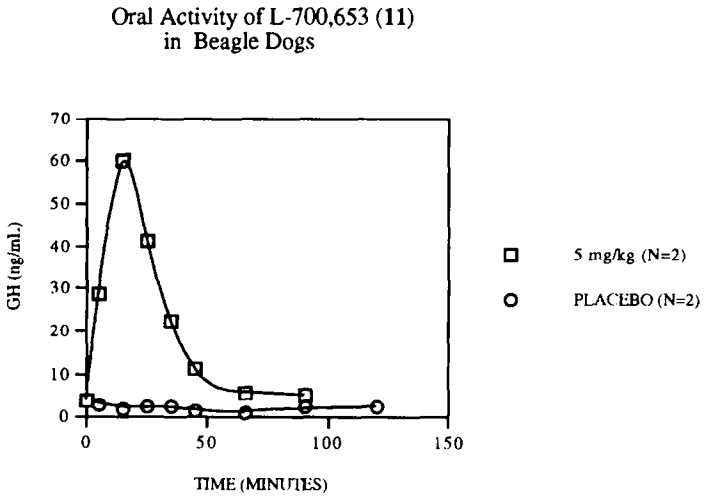
**Table 2**



| Compound | R | $ED_{50}$ (μM)[a] |
|---|---|---|
| **2** | $NH_2$ | **0.08** |
| **17** | $NHCH_2CH_2OH$ | **3** |
| **18** | $NHCH_2CH_2CH_2OH$ | **0.4** |
| **19** | $NHCH_2CH_2CH_2CH_2OH$ | **0.01** |
| **20** | $NHCH_2CH_2CH_2CH_2CH_2OH$ | **0.01** |
| **21** | $NHCH_2CH_2CH_2CH_2CH_3$ | **> 1** |

[a] **Rat pituitary cell assay.**

Substitution of the amino acid side-chain of L-692,429 with either the (R)-2-hydroxypropyl group, compound **7** (L-692,585)[4,7], or the 2(S),3-dihydroxypropyl group, compound **10**[7], leads to a significant increase in potency (Table 3). The same substitutions are also effective for increasing the potency to less than 10nM for the 2'-carboxamide class of benzolactam GH secretagogues as shown for 2-(R)-hydroxypropylamine analog **8** and 2(S),3-dihydroxypropylamine analog **11**. The most potent carboxamide in this series, L-700,653 (**11**), was tested orally in beagle dogs and found to be active in releasing growth hormone (30-fold GH elevation over basal levels) at a dose of 5 mg/kg.[8]



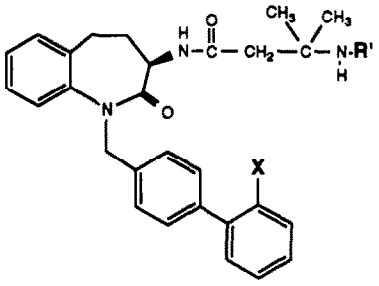
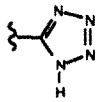
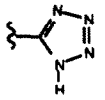
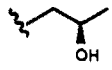
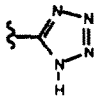
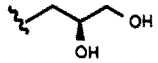
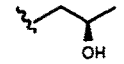
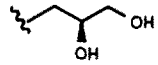


Table 3

| Entry | X | R' | $ED_{50}$ (nM)[a] |
|---|---|---|---|
| L-692,429 (1) |  | H | 60 |
| 7 |  |  | 3 |
| 10 |  |  | 10 |
| 2 | $CONH_2$ | H | 80 |
| 8 | $CONH_2$ |  | 4 |
| 11 | $CONH_2$ |  | 3 |

[a] Rat pituitary cell assay.


## Summary

The structure-activity relationships of the carboxamide series of growth hormone secretagogues have been explored. Small *N*-alkyl substitution of the 2'-carboxamide is tolerated while large *N*-alkyl substitution is detrimental to *in vitro* GH releasing activity. Interesting structure-activity relationships are observed for the ω-hydroxyalkyl carboxamide analogs with an increase in potency observed when the terminal hydroxyl group is placed four to five carbon atoms away from the carboxamide moiety. Substitution of the amino acid side chain with an (R)-2-hydroxypropyl group or 2(S),3-dihydroxypropyl group results in a large increase in potency. A potent carboxamide analog which contains the dihydroxypropyl amine side chain, L-700,653 (**11**), is active at an oral dose of 5mg/kg in beagle dogs. An orally active GH secretagogue may offer a significant clinical advantage over rhGH[9], which is routinely administered by intramuscular injection. Further studies on L-700,653[10], as well as other structure-activity relationships of the benzolactam series of growth hormone secretagogues will be disclosed later.



## Acknowledgment

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**References and Notes**

1. a) DeVita, R.J.; Schoen, W.R.; Ok, D.; Barash, L.; Brown, J.E.; Fisher, M.H.; Hodges, P.; Wyvratt, M.J., Jr.; Cheng, K.; Chan, W.W.-S.; Butler, B.S.; Smith, R.G. *BioMed. Chem. Lett.* **1994**, *4*, 1807-1812.
b) Schoen, W.R.; Pisano, J.M.; Prendergast, K.; Wyvratt, M.J., Jr.; Fisher, M.H.; Cheng, K.; Chan, W.W.-S.; Butler, B.; Smith, R.G.; Ball, R.G. *J. Med Chem.* **1994**, *37*, 897-906.

2. All final compounds were purified by reverse phase medium pressure liquid chromatography on C-8, characterized by $^1$H NMR, MS and elemental analysis and tested as trifluoroacetate salts.

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5. Hertel, L.W.; Grossman, C.S.; Kroin, J.S. *Synth. Commun.* **1991**, *21*, 151-154.

6. Cheng, K.; Chan, W.W.-S.; Barreto, A.; Convey, E.M.; Smith, R.G. *Endocrinology* **1989**, *124*, 2791-2798. GH releasing activities of compounds presented in Tables 1-3 have been normalized to L-692,429 ($ED_{50}$ = 0.06μM).

7. Ok, D.; Schoen, W.R.; Hodges, P.; DeVita, R.J.; Brown, J.E.; Cheng, K.; Chan, W.W.-S.; Butler, B.S.; Smith, R.G.; Fisher, M.H.; Wyvratt, M.J. manuscript in preparation.

8. Beagle dogs (average weight of 15kg) were dosed with an aqueous solution (5mL/kg; native pH) of L-700,653 trifluoroacetate salt by oral gavage. Blood samples were taken before administration of drug and at 15 minute intervals; GH levels of the sera determined by RIA.[6]

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