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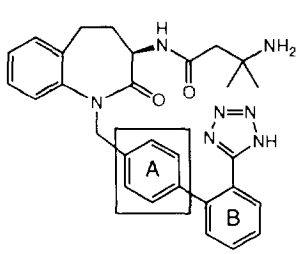
ALIPHATIC REPLACEMENTS OF THE BIPHENYL MOIETY OF THE NON-PEPTIDYL GROWTH HORMONE SECRETAGOGUES L-692,429 AND L-692,585

Lin Chu*, Helmut Mrozik, Michael H. Fisher, Jeannette E. Brown, Kang Cheng, Wanda W.-S. Chan, William R. Schoen†, Matthew J. Wyvratt, Bridget S. Butler and Roy G. Smith

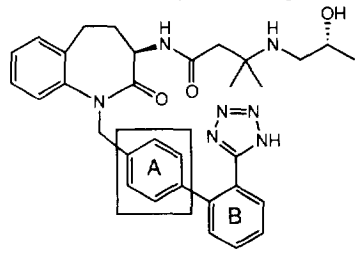
Departments of Medicinal Chemistry and Biochemistry & Physiology
Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065 USA

Abstract: Replacement of the central phenyl ring of the biphenyl moiety in the novel growth hormone (GH) secretagogues L-692,429 and L-692,585 with partially or completely saturated surrogates has been investigated. The cyclohexenyl analogue **37** displayed GH releasing activity comparable to L-692,585, indicating that the aromaticity of this central ring is not critical for bioactivity and that this ring may serve primarily to orient the benzolactam and phenyltetrazole pharmacophores.

Introduction: Recently, there has been extensive clinical research on growth hormone (GH) therapy, targeting for example, potential reversal of some of the bodily changes associated with aging,[1] growth promotion in GH-deficient children, and prevention of osteoporosis.[2] Administration of a growth hormone secretatogue to stimulate GH release has been proposed to be more advantageous than treatment with recombinant human GH for reasons such as cost, convenience, and oral activity.[3,4,5] Among reported GH secretagogues, non-peptidyl benzolactams such as L-692,429 (**1**)[3,5-8] and L-692,585 (**2**)[5,9] have been of particular interest because of their high potency and selectivity. To understand the contribution of the biphenyl region of **1** and **2** to their GH releasing activity, a series of analogues were investigated. This Communication describes modifications in the biphenyl region and, in particular, that the aromaticity of the **A** ring is not critical for bioactivity, thus suggesting that it may serve primarily to orient the benzolactam and phenyltetrazole pharmacophores.



1 (L-692,429)
ED_{50} = 60 nM

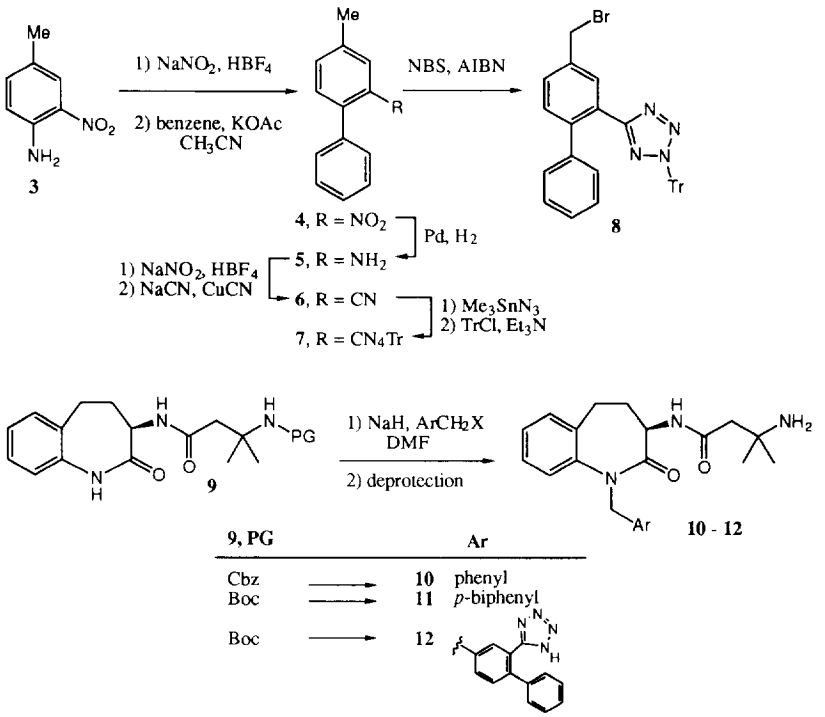


2 (L-692,585)
EC_{50} = 3 nM

Synthesis: The syntheses of analogues **10** - **12** with modified or "truncated" aryl groups in the biphenyl region of L-692,429 (**1**) are outlined in Scheme I. The synthesis of the common intermediate **9** has previously been reported.[6] For **10** and **11**, the commercial benzyl bromide and 4-chloromethylbiphenyl were used in the key alkylation steps,[5,6] followed by suitable deprotection conditions (TFA/CH_2Cl_2 for Boc and Pd/H_2 for Cbz). For compound **12**, which has the tetrazole moiety connected to the **A** ring instead of the **B** ring as in **1**, more

elaborate chemical transformations were required to prepare the alkylating reagent **8** (Scheme I). All final products reported here were purified by reverse phase (C8) chromatography (MPLC).

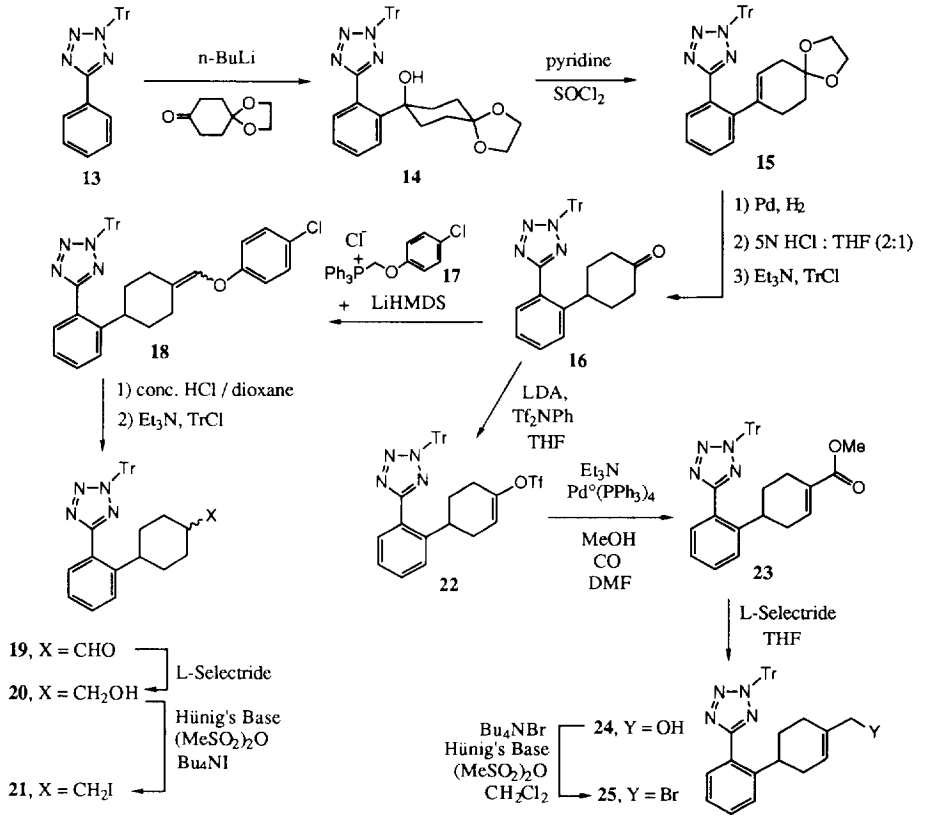
Scheme I



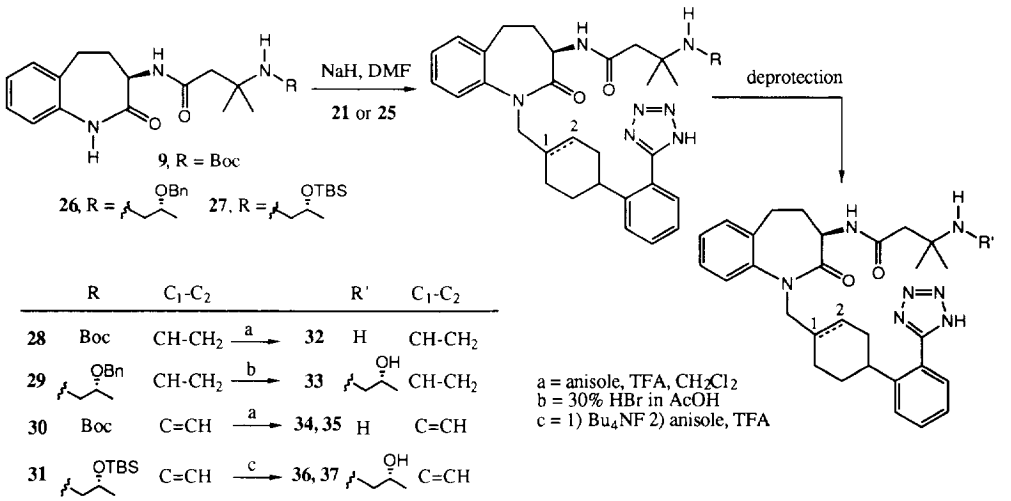
The syntheses of the cyclohexyl analogues **32** and **33** are outlined in Schemes II and III. Treatment of triphenylmethyl(trityl)-protected phenyltetrazole[10] (**13**) with n-BuLi resulted in the formation of the ortho-lithiated species,[11] which upon condensation with cyclohexanedione mono-ethylene ketal led to the tertiary alcohol **14**, which was subsequently dehydrated to form olefin **15**.[12] Hydrogenation (Pd/H2) of olefin **15** followed by acidic hydrolysis and re-protection of the tetrazole group afforded cyclohexanone **16** in 80% yield (3 steps). Wittig reaction of **16** with phosphonium salt **17**, obtained by reacting α,4-dichloroanisole with triphenylphosphine, acid hydrolysis of the resulting vinyl ether, and re-protection resulted in the homologated compound **19**, which was reduced with L-Selectride at low temperature (-25 °C to room temperature). Conversion to the mesylate followed by *in situ* displacement with Bu4NI in CH_2Cl_2 (reflux overnight) generated the iodide **21**, which was coupled to different benzolactams[5,6,9] (Scheme III) using the previously reported reaction conditions.

Cyclohexanone **16** could also be transformed to produce cyclohexenyl analogues **34** through **37** (Schemes II, III). Enolization of **16** with LDA followed by trapping with N-phenyltrifluoromethane-sulfonimide generated the vinyl triflate **22**. Under a steady carbon monoxide atmosphere (balloon filled), Et3N,

Scheme II



Scheme III



	R	C_1-C_2		R'	C_1-C_2
28	Boc	CH-CH_2	a →	32 H	CH-CH_2
29	OBn	CH-CH_2	b →	33 OH	CH-CH_2
30	Boc	C=CH	a →	34, 35 H	C=CH
31	OTBS	C=CH	c →	36, 37 OH	C=CH

catalytic amount of Pd°, and excess MeOH, **22** was carbonylated to form methyl ester **23**, which was subsequently reduced with L-Selectride (-78 °C to -40 °C) and converted to the corresponding bromide **25**.

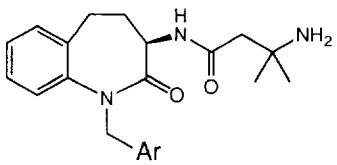
The protecting group on benzolactam **26** was changed from benzyl to tert-butyldimethylsilyl(TBS) because of the anticipated incompatibility of the olefin with the conditions required for debenzylation (Scheme III). The coupled product **31** was deprotected stepwise with Bu_4NF and the aforementioned TFA condition, since the TBS group was shown to be stable under TFA/CH_2Cl_2 or TsOH/MeOH conditions.

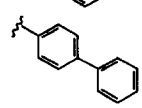
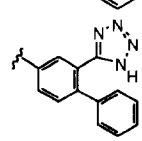
Results and Discussion

Growth hormone release *in vitro* was determined in rat pituitary cells as previously described.[13] Truncated analogues **10** and **11** (Table I) are weakly active when compared to L-692,429, as is the isomeric biphenyl tetrazole analogue **12**. These analogues illustrate the strict spacial requirement for a tetrazole moiety appropriately positioned on the biphenyl subunit for potent GH releasing activity. Primarily for this reason, the second ring (**B** ring) of the biphenyl region was maintained intact, and the effects of cyclohexyl and cyclohexenyl replacements of the first ring (**A** ring) were probed. Table II depicts these analogues and the corresponding *in vitro* GH releasing data.[14]

As anticipated from earlier work,[5,9] the 2-hydroxypropyl analogues **2**, **33**, **36**, and **37** are intrinsically more potent than their unsubstituted amino counterparts **1**, **32**, **34**, and **35**, regardless of the degree of unsaturation in the lower region of the molecule (Table II). The GH secretagogue activity is less dependent on the aromaticity of the linker **A** ring connecting the benzolactam and phenyltetrazole moieties than originally expected. While cyclohexyl analogues **32** and **33** are significantly less active than their aromatic counterparts **1** and **2**, respectively, the cyclohexenyl derivatives **35** and **37** are both very potent secretagogues approaching the GH releasing activities of **1** and **2**. In addition, cyclohexenyl analogues **35** and **37** are more potent than their

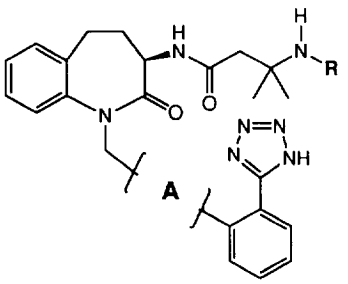
Table I

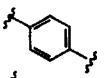
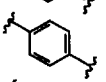
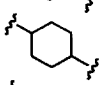
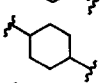
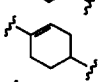
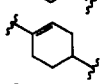
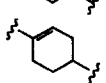
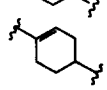


Compound	Ar	ED_{50} (μM)
10		7
11		3
12		>1[a]

[a] Weakly active at 1 μM

Table II



Compound	R	A	ED_{50} (nM)
1 (L-692,429)	H		60
2 (L-692,585)			3
32	H	 a	860
33		 a	75
34	H	 b	1200
35	H	 c	120
36		 b	25
37		 c	7

[a] mixture of two diastereomers
[b] single diastereomer, Isomer A (faster-moving isomer)
[c] single diastereomer, Isomer B (slower-moving isomer)

isomeric analogues **34** and **36**, respectively. These results suggest that the aromaticity of the internal **A** ring is not critical for bioactivity, and this ring may serve primarily as a scaffold for positioning the benzolactam and phenyltetrazole pharmacophores, which is in agreement with the reported molecular modeling of L-692,429 and the growth hormone releasing hexapeptide GHRP-6.[6] However, it must be kept in mind that cyclohexyl and phenyl groups have been shown to interact similarly with certain aromatic groups.[15] It is therefore possible that the phenyl and cyclohexenyl subunits discussed here display weak but significant interaction with the receptor.

In summary, the aromaticity in the linker **A** ring of the biphenyl moiety has been shown not to be critical for GH secretagogue activity and that its primary function may be to position the benzolactam and phenyltetrazole pharmacophores for optimal interaction with the receptor. Additional surrogates for the biphenyl moiety in **1** and **2** will be reported in the near future.

Acknowledgement

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† Current Address
Institute for Chemistry
Miles, Inc.
400 Morgan Lane B24
West Haven, CT 06516-4175

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