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THE DESIGN AND SYNTHESIS OF ORALLY ACTIVE SHORT DURATION SPIROINDANE GROWTH HORMONE SECRETAGOGUES

James R. Tata,*[a] Zhijian Lu,[a] Thomas M. Jacks,[b] Klaus D. Schleim,[b] Kang Cheng,[b] LienteWei,[b] Wanda W.-S. Chan,[b] Bridget Butler,[b] Nancy Tsou,[c] Kwan Leung,[d] S.-H. L. Chiu,[d] Gerard Hickey,[b] Roy G. Smith,[b] and Arthur A. Patchett[a]

Departments of Medicinal Chemistry,[a] Biochemistry and Physiology,[b] Molecular Design & Diversity[c] and Drug Metabolism,[d] Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

Abstract: The design, synthesis, and activities of a series of short duration spiroindane growth hormone secretagogues are reported. Incorporation of a readily metabolized ester into the spiroindane benzylic position provided a series of highly potent orally active secretagogues with a short duration of action.
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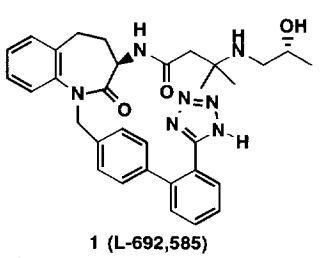
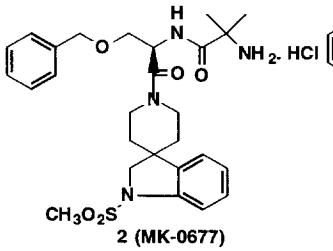
Recent reports have detailed the discovery and optimization of spiroindane growth hormone (GH) secretagogues.[1-4] Clinical studies have shown that these peptidomimetic GH secretagogues promote the release GH in man.[5] GH secretagogeus may have advantages over bolus GH therapy in that they more closely mimic the natural pulsatile release of GH.[6] A down-regulation of GH release is observed upon chronic dosing of the long duration secretagogue **2** (**MK-0677**) and **2** causes a prolonged and dramatic increase in IGF-1 levels.[7] In contrast, neither down-regulation nor potentiation of GH release occurs upon chronic dosing of the short duration secretagogue **1** (**L-692,585**) in beagles.[8] Furthermore, **1** only causes transient increases in IGF-1 levels. It is not known to what extent the beneficial physiological effects of GH are mediated by the direct interaction of GH with its receptors in tissues vs indirect effects through the subsequent release of its mediator IGF-1.[9] To explore further the properties of a short acting secretagogue, it was desirable to have one that was orally active. Because of the poor oral absorption of **1** and its close analogs, modifications of the orally active spiroindanes were carried out. Two approaches toward a short duration compound were contemplated: metabolism of an active compound to an inactive metabolite and metabolism of the active compound to a rapidly cleared metabolite. This paper reports the design of a new short acting orally active spiroindane secretagogue **3** (**L-163,833**), based on the latter approach, and some of its effects on GH and IGF-1 levels.



1 (L-692,585)



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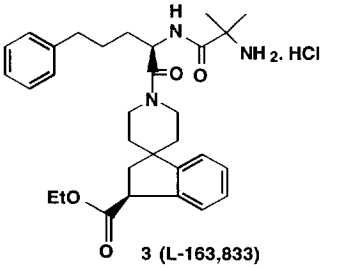


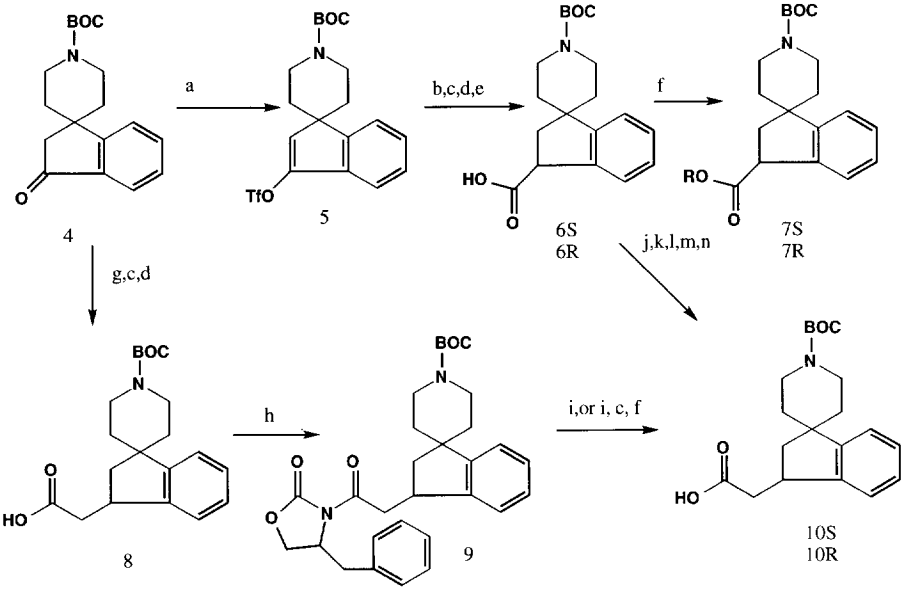
3 (L-163,833)

Chemistry

Chemistry

Ketospiroindane **4** was readily converted into the desired substituted spiroindane intermediates as shown in Scheme 1. Carboxylation of vinyl triflate **5** followed by hydrogenation and hydrolysis gave racemic acid **6**. The resolution of **6** was accomplished with (*R*)- or (*S*)-methylbenzylamine. Optical purity was determined by HPLC analysis (Chirocel OD) and the absolute configuration was determined by single crystal X-ray analysis of the crystalline salt.[10] The higher homolog was prepared from the ketone via an Horner–Emmons reaction followed by hydrogenation and hydrolysis. Resolution of the racemic acid was accomplished by attaching (*S*)-4-benzyl-2-oxazolidinone to it and separating the diastereomers by preparative MPLC. Conversion to the desired acid was accomplished in the usual manner.[11] Alternatively, homologation of the resolved acid (3*R*)- or (3*S*)-, as shown, gave the optically pure homologs with the advantage of known absolute stereochemistry.

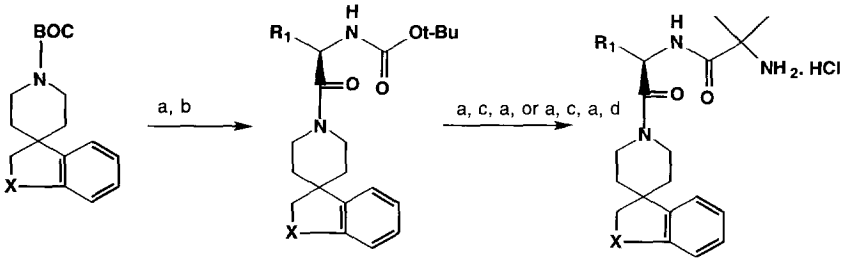
Scheme 1



Reagents and condititons: (a) $KN(TMS)_2$, N-Phenyltrifluromethanesulfonimide, THF; (b) $Pd(OAc)_2$, CO, Et_3N, DMF, EtOH; (c) Pd/C, H_2; (d) NaOH, EtOH; (e) (*R*)- or (*S*)-benzylmethylamine, toluene; (f) ROH, EDC, DMAP, CH_2Cl_2; (g) triethyl phosphonoacetate, $KN(TMS)_2$, THF; (h) (*S*)-4-benzyl-2-oxazolidinone, BuLi, Et_3N, ethylchloroformate, THF; (i) BnOLi, THF; (j) BH_3-THF; (k) TsCl, Et_3N; (l) NaCN, DMSO; (m) 2 N HCl, 100 °C; (n) $(Boc)_2O$, 1 N NaOH, dioxane.

Elaboration of the optically active intermediates into the final secretagogues was accomplished via standard peptide coupling/deprotection reactions as shown in Scheme 2 below. The acids were prepared in one additional step by reductive removal of the benzyl ester.

Scheme 2



x = CH_2, CHCOOR, $CHCH_2COOR$

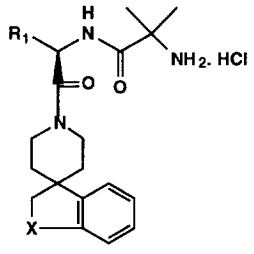
Reagents and conditions: (a) EtOAc/HCl; (b) Boc-amino acid, EDC, HOBT, NMM, CH_2Cl_2; (c) Boc-α-methylalanine, EDC, HOBT, NMM, CH_2Cl_2; (d) Pd/C, H_2, EtOH.

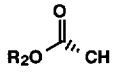
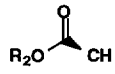
Results and Discussion

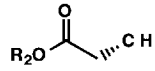
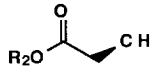
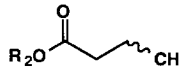
The compounds were evaluated for their ability to release growth hormone in the rat pituitary cell assay.[12] As with other polar groups,[1,4] incorporation of an ester or acid into the benzylic position of the spiroindane greatly increases potency, see Table 1 below. For example, comparing the ester with the unsubstituted parent (**18** vs. **11** and **3** vs. **12**) shows a six to tenfold increase in potency. This potency gain is observed for both stereoisomers although there is a small but consistent preference for the (*S*)- isomer in the shorter series (compare **3** and **15**) and the (*S*)- isomer in the longer homolog series (**22** vs. **26**). Also the potency gain is remarkably tolerant of chain length. For example, **3** and its longer homologs **22** and **29** all have similar potencies. Since it was assumed that the dramatic increase in potency was due to a specific interaction of the ester with the receptor, the independence of that gain from stereochemistry and chain length, was unexpected. In all cases the acids were only slightly less potent than the esters (**3** vs. **20**).

Selected compounds were evaluated for their GH releasing ability in the beagle dog model[13] summarized in Table 2. The minimum effective dose that caused at least a four-fold increase in serum GH levels was considered a positive response and was used to compare invivo potencies. In general the enhanced in vitro potencies of the polar spiroindanes were reflected in their improved in vivo activities. The GH releasing ability of ester **3** on oral dosing is better than that of the unsubstituted parent **12** and approaches that of **2**. The longer homologs also possess good oral activity as demonstrated by **22**. In general the acids were slightly less active when dosed orally than were the corresponding esters (compare ester **3** and its acid **20** and ester **22** and its acid **23**).

Table 1



Entry	R1	X		EC_{50} (nM)
2	benzyloxymethyl-	NSO_2CH_3		1.5
11	benzyloxymethyl-	CH_2		17
12	phenylpropyl-	CH_2		10
13	3-indolylmethyl	CH_2		14
				
14	benzyloxymethyl-	R_2 =	Et	6.6
15	phenylpropyl-		Et	2.0
16	phenylpropyl-		H	2.5
17	3-indolylmethyl		Et	8.3
				
18	benzyloxymethyl-	R_2 =	Et	2.9
19	benzyloxymethyl-		H	4.4
3	phenylpropyl-		Et	1.0
20	phenylpropyl-		H	2.1
21	3-indolylmethyl		Et	6.0

Entry	R1	X		EC_{50} (nM)
				
22	phenylpropyl-	R_2 =	Et	0.8
23	phenylpropyl-		H	1.9
24	3-indolylmethyl		Et	7.0
25	3-indolylmethyl		H	5.8
				
26	phenylpropyl-	R_2 =	Et	1.0
27	phenylpropyl-		H	2.3
28	3-indolylmethyl		Et	28
				
29	phenylpropyl-	R_2 =	Et	1.3
30	phenylpropyl-		H	2.5

(a) Data from the rat pituitary cell assay.[12] All EC_{50} are normalized against standards, either **L-692,429** EC_{50} 60 nM or **L-692,585** EC_{50} 3.0 nM.

Table 2

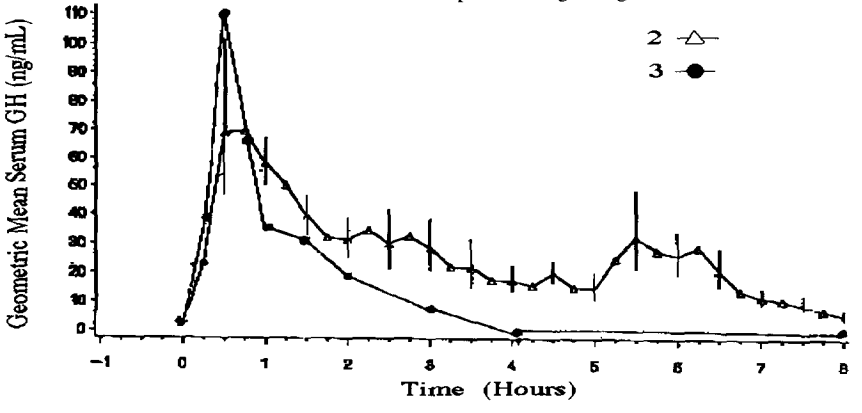
	DOG GH Release		
Entry	iv (mpk)	po (mpk)	Resonders[a]
2	0.025	0.125	6/8
		0.25	8/8
3	0.005	0.125	1/2
		0.25	5/8
20		1.0	1/1
		0.5	1/2
22		0.25	2/5
		0.5	4/4
23		0.5	2/2

[a]Doses shown represent the lowest dose where fourfold elevations over basal GH levels were observed.

Having demonstrated good oral activity in this series we examined the duration of action aspect next. Since the acids had similar potency to the esters, metabolism to an inactive metabolite was not applicable here. However, as Figure 1 shows, esters do have a shorter duration of action than does **2** following oral administration to dogs at 1 mpk. For example GH levels approach baseline in dogs treated with **3** in 2 hours while GH levels are still elevated 6-8 hours after an equivalent dose of **2**.

Figure 1

Geometric Mean Serum GH Concentrations (SE) After Oral Administrations of either **2** or **3** @ 1 mpk to 6 Beagle Dogs



Chronic oral dosing of **3** at either 0.5 mpk or 1.0 mpk produced moderate increases in IGF-1 (45–65%) accompanied by a decreased GH response as seen in Table **3**.[14] Due to the limited number of animals in the study it is not possible at this time to determine if there is a direct correlation between duration of action, the observed down-regulation of GH response and IGF-1 levels.

Table 3

Dose (mpk)	Day	GH AUC (ng/mL.h)[a]	GH % of Day 1 response[a]	IGF-1 % increase[a]
1.0	Day 1	134.6		
	Day 4	108.6	80%	+45%
0.5	Day 1	122.48		
	Day 4	78.4	65%	+65%

[a]Average value (n = 3).

Additional studies have shown that **3** is rapidly converted to its acid **20** in vitro (rat, dog, human plasma, and liver microsomes) as well as in vivo (rat and dog).[15] It has also been shown that **20** is rapidly cleared resulting in a relatively short half life (t1/2 = 1.7 h vs. 4.8 h for **2**) thus explaining its shorter duration of action.[15] Although the absorption of **3** was good, >50% (rat), the bioavailability was only moderate 11.8% (dogs) and 4.5% (rats) reflecting its high rate of clearance.

Summary

We have shown that incorporation of an ester into the spiroindanes gives a new series of orally active secretagogues. This series takes advantage of the efficient hydrolysis of esters to provide the desired short duration of action. Details of in vivo studies with these compounds will be reported in due course.

Acknowledements

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