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Highly potent growth hormone secretagogues

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Abstract—During an effort to search for more potent growth hormone secretagogues, we discovered a class of compounds of which the best compound **8** was 7-fold more active in vitro than the best compound in the series we revealed before [Tata, J. R.; Lu, Z.; Jacks, T. M.; Schleim, K. D.; Cheng, K.; Wei, L.; Chan, W.-S.; Butler, B.; Tsou, N.; Leung, K.; Chiu, S.-H. L.; Hickey, G. J.; Smith, R. G.; Patchett, A. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2319.]. Animal studies show that compound **8** can stimulate growth hormone release at the oral dose as low as 0.06 mpk. Chemistry and biological studies are discussed.

Growth hormone secretagogues were the subject of intensive studies in past years due to their potential in the clinic.[1] In the previous communication, we described a class of short acting growth hormone secretagogues that were orally active (represented by ester L-163,833).[2] We were also interested in studying long duration compounds that might closely mimic the natural pulsatile release of GH based on our clinic data from MK-0677,[1j] another long duration secretagogue. In this communication, we describe a series of potent long duration spiroindane growth hormone secretagogues in which the best compound **8** shows excellent in vitro and in vivo activity (Fig. 1 and Scheme 1).

The synthesis of this class of compounds started from chiral acid **18**. Compound **18** and some related intermediates were discussed previously.[2] Acid **18** was coupled with benzyl alcohol to afford benzyl ester **19** in 75% yield. Acidic cleavage of the Boc group followed by EDC coupling with Boc-phenylpropyl amino acid gave **20** in 83% yield. Treatment of **20** with TFA and EDC coupling of N-Boc α-methylalanine afforded compound **21** (87%). Final compounds were obtained by catalytic hydrogenolysis and subsequent EDC coupling with amine RNH_2 and acidic cleavage of the Boc group (50–80%). All amines RNH_2 were commercially available.

All the compounds were evaluated for their ability to stimulate growth hormone in the rat pituitary cell assay.[3] In our earlier article, we discussed that an ester analog was a short acting secretagogue of GH.[2] In order to find alternative long duration GH secretagogues, we decided to test if an amide analog in this series would be of a longer duration of action in vivo. We first examined the primary amides. Both enantiomer **1** and **12** are very potent. In fact, they are the most active analogs in the respective series. The *R* isomer **1** is 4-fold more potent than the *S* isomer **12**. In general, the *R* isomers are more active than the corresponding *S* isomers.

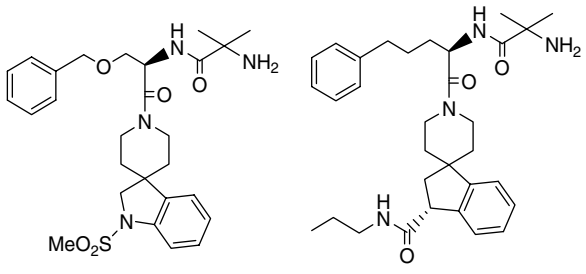

Figure 1. Potent growth hormone secretagogues.

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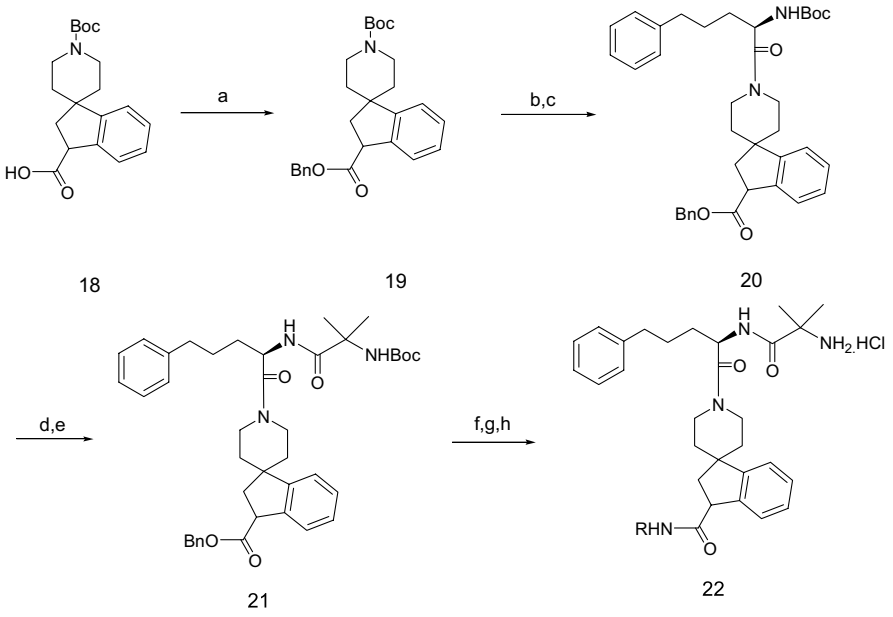
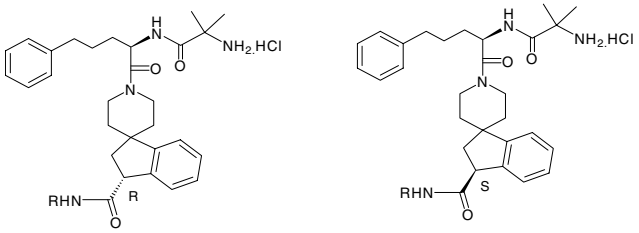


Scheme 1. Reagents: (a) BnOH, EDC, NMM,CH_2Cl_2; (b) TFA, CH_2Cl_2; (c) Boc-phenylpropyl amino acid, EDC, HOBT, NMM,CH_2Cl_2; (d) TFA, CH_2Cl_2; (e) N-Boc-α-methylalanine, EDC, HOBT, NMM,CH_2Cl_2; (f) Pd/C, H_2, MeOH; (g) RNH_2, EDC, NMM,HOBT, CH_2Cl_2; (h) EtOAc/HCl.

In a series of *R* isomers, extension of the chain length results in a potency improvement. The 3-carbon straight chain is optimal. The propyl amide **8** is as potent as the allyl analog (**10**). However, the branched *i*-Pr amide **11** is 2-fold less potent than **8**. Introduction of a terminal hydroxyl group at the carbon chain affords very active analogs and their potency seems insensitive to the length change of the chain (**4**–**6**). Replacement of the hydroxyl with methyl sulfonamide results in a better GH secretagogue (**7**). Bulky groups like phenyl cause a drop in potency (**9**). The *S* isomer series displays a similar trend (**13**–**17**). One interesting observation is that the *R* isomers of the amides are more active than the corresponding *S* isomers; however, the *S* isomers of the esters are more potent than the *R* isomers instead.[2] Due to insufficient structural information at the receptor level, it was unclear why the ester series showed a different SAR from the amide series. Nonetheless, in general, the amides are more active than the esters. The SAR of these amides is summarized in Table 1. For comparison, the data for the ester analogs can be referred to our earlier paper.[2]

Table 1. SAR studies of amide analogs in the in vitro assay



Compound	R	EC_{50} (nM)	Compound	R	EC_{50} (nM)
1	H	0.09	**12**	H	0.35
2	Me	0.4	**13**	Me	3.8
3	Et	0.9	**14**	Et	2.1
4	$-(CH_2)_2OH$	0.51	**15**	$-(CH_2)_2OH$	0.45
5	$-(CH_2)_3OH$	0.41	**16**	$-(CH_2)_3OH$	0.85
6	$-(CH_2)_4OH$	0.44	**17**	$-(CH_2)_4OH$	0.73
7	$-(CH_2)_2NHMs$	0.21			
8	Pr	0.15	MK-0677		1.5
9	Ph	1.2	L-163,833		1.0
10	Allyl	0.14			
11	*i*-Pr	0.3			

Data from the rat pituitary cell assay. All EC_{50} are normalized against our internal standards. Single data point.

Table 2. In vitro response of growth hormone secretagogues

Compound	Dog GH release		Responders[a]
	iv (mpk)	po (mpk)	
1		0.25	4/4
2		0.125	5/6
3	0.10	0.25	6/7
4		0.50 (weak)	4/4
8	0.01	0.06	6/6
MK-0677	0.025	0.125	8/10

[a] Doses shown represent the lowest dose where 4-fold elevations over basal GH levels were recorded.

Five compounds in the *R* isomer series were evaluated in vivo for their ability to stimulate the release of GH in beagle dog model as summarized in Table 2. The minimum effective dose that caused at least a 4-fold increase in serum GH levels was regarded as a positive response. In general, the alkyl amides responded better than the more polar analogs (**2**, **3** and **8** vs **1** and **4**). Compound **8** (the propyl analog) performed the best compared to the shorter chain analogs (Me analog **2** and Et analog **3**). Another observation we had during the study of this class of compounds was that the female animals generally responded better than the male counterpart. All compounds tested in vivo have a long duration of action. The GH levels remain well above the basal level even after 2 h. In case of the short acting series, the level of GH returned to the base line after 1.5 h.[2] In the same assay, compound **8** showed similar duration of action to MK-0677 at 1 mpk. There was no follow-up chronic study for these compounds. Therefore it remains unclear whether these amide analogs would mimic the natural pulsatile release of GH or affect IGF-I level in vivo. Compared to MK-0677, compound **8** is 10-fold more potent in vitro and 2-fold more potent in vivo.

In summary, a new class of potent GH secretagogues has been reported. The best compound **8** is not only highly potent in the rat pituitary cell assay but also orally active at a very low dose in dogs to stimulate growth hormone.

Acknowledgments

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