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POTENT 3-SPIROPIPERIDINE GROWTH HORMONE SECRETAGOGUES

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Abstract: Systematic SAR studies of the different regioisomers and homologues of the spiro(indane-1,4'-piperidine) moiety in the growth hormone secretagogue L-162,752 are presented. Among them, spiro(3*H*-1-benzopyran-2,3'-piperidine) was found to afford secretagogues with low nanomolar in vitro activity.

Introduction: Growth hormone releasing peptides (GHRP), which are a series of synthetic hexa- or heptapeptides derived from Met-enkephalin, stimulate the release of GH in the pituitary gland.[1] GHRPs such as GHRP-6 and their small organic molecule mimetics such as L-692,429 (Figure 1)[2] are generally referred to as growth hormone secretagogues (GHS). They exert their stimulatory effect through a different mechanism than the endogenous growth hormone release hormone (GHRH).[3] GHS act through a recently discovered G-protein coupled receptor (GHSr),[4] for which no natural ligand has yet been discovered. Recent clinical studies with GHRP-6, hexarelin, and the nonpeptide benzolactam biphenyl GHS, L-692,429 have demonstrated that stimulation of GH release could be an alternative for GH replacement therapy. Unfortunately, they lack good oral bioavailability. The discovery in these laboratories of spiro(indane-1,4'-piperidine) class of GHS, by an approach involving derivatization of "privileged structures" generated a potent and orally active clinical candidate L-163,191 (MK-0677, Figure 1).[5] The lead optimization process for MK-0677 has been detailed in a series of papers.[6] Herein we report our concurrent progress made by the replacement of the 4-spiroindane with a series of novel and potent 4- and 3- spiropiperidine based GHS.

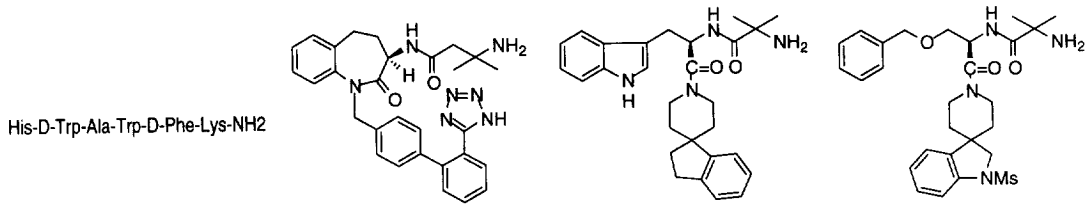

Figure 1

Chemistry: The discovery of the spiro(indane-1,4'-piperidine) (**1**) class of GHS spurred our interest in finding other novel structures for patentability and possible biological profile variations. A logical approach was to study the effect of different ring sizes and arrangements. The following spiropiperidines (Figure 2) were

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designed and synthesized as part of the SAR studies for comparison with the original spiroindane **1**. The spirobenzopyrans (**4**, **7**) were chosen over their all carbon analogues for their easier chemical accessibility.

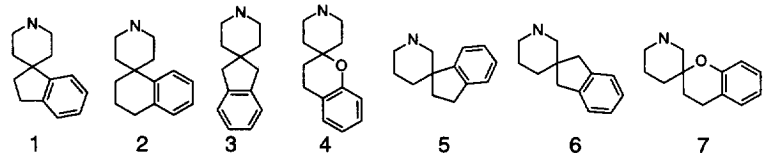
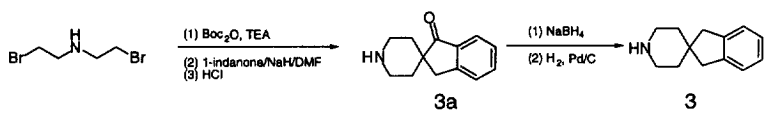


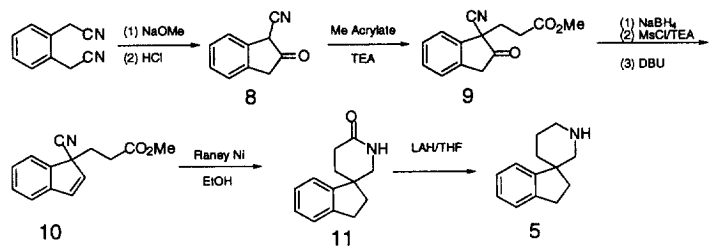
Figure 2

Methods for preparing the different spiropiperidine systems are illustrated in the following schemes. 3,4-Dihydrospiro(naphthalene-1(2*H*),4'-piperidine) (**2**) is a known compound.[7] A direct alkylation approach was taken for the synthesis of 1,3-dihydrospiro(indene-2,4'-piperidine) (**3**). Although the spiroindane **1** was prepared by alkylation of indene with bis(2-chloroethyl)amine *t*-butyl carboxylate,[7] similar conditions gave little product with 1-indanone, presumably due to the unreactive nature of the chloride and much higher basicity of the enolate. Replacing the alkylating reagent with bis(2-bromoethyl)amine *t*-butyl carboxylate,[8] however, gave the desired spiropiperidine in high yield after removal of the Boc protecting group. Reduction of the resulting ketone **3a** with sodium borohydride and hydrogenolysis of the resulting benzylic alcohol afforded the desired piperidine intermediate **3** (Scheme 1).



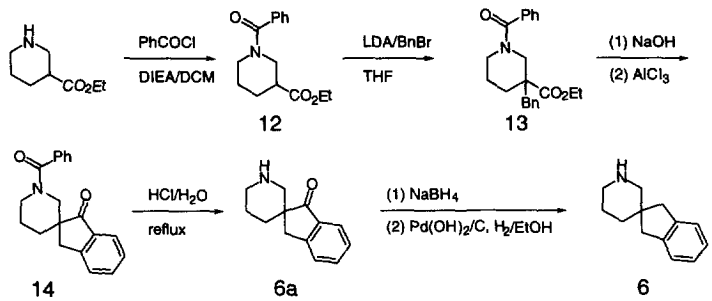
Scheme 1

The synthesis of the 2,3-dihydrospiro(1*H*-indane-1,3'-piperidine) (**5**) is shown in Scheme 2. *o*-Xylenedinitrile was treated with sodium methoxide and the resulting imine was hydrolyzed to give 1-cyano-2-indanone (**8**). Michael addition to methyl acrylate in the presence of triethylamine gave an adduct **9**, setting the stage for intramolecular cyclization. Reduction of the ketone followed by mesylation and elimination gave an indene **10**. Subsequent Raney-Ni catalyzed reduction (1000 psi, 100 °C, 8 h), resulted in three reactions in one pot (reduction of the olefin, reduction of the nitrile to amine and subsequent intramolecular closure) to provide the desired lactam **11** in high yield. LAH reduction of the lactam gave the desired piperidine intermediate **5**.



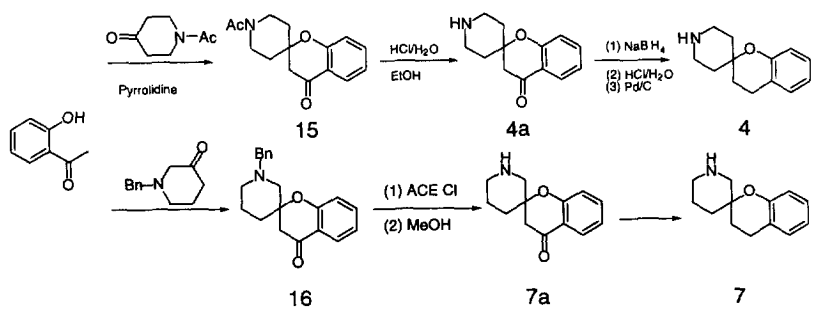
Scheme 2

The synthesis of the 1,3-dihydrospiro(indene-2,3'-piperidine) (**6**) is more straight forward and is shown in the Scheme 3. Ethyl nipecotate was protected as a benzamide **12**. Alkylation of the position α- to the ester with benzyl bromide provided the quaternary carbon intermediate **13**. Saponification of the ethyl ester followed by Friedel-Crafts cyclization provided the desired spiro ring system **14**. The benzoyl protecting group was removed by acid hydrolysis, and the ketone **6a** was reduced, as before, to afford the desired spiropiperidine **6**.



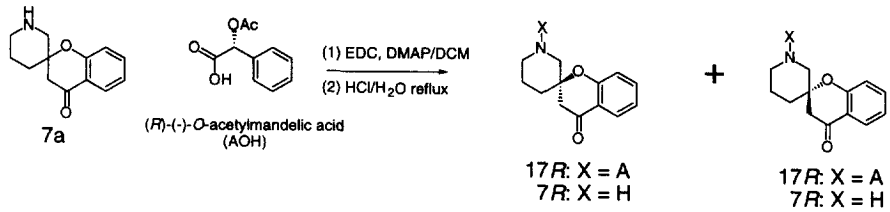
Scheme 3

Spiro(2*H*-1-benzopyran-2,4'-piperidine) (**4**) was easily prepared by pyrrolidine catalyzed reaction between 2-hydroxyacetophenone and the commercially available *N*-acetyl-4-piperidinone.[9,10] Acidic hydrolysis of the acetamide by refluxing in hydrochloric acid afforded the piperidine **4a**. Reduction of the ketone was carried as before to yield the benzopyran intermediate **4**. The regioisomer spiro(3*H*-1-benzopyran-2,3'-piperidine) (**7**) was prepared similarly from the commercially available *N*-benzyl 3-piperidone. Removal of the benzyl protecting group was best accomplished by α-chloroethyl chloroformate (ACE-Cl)[11] to provide the benzopyranone.



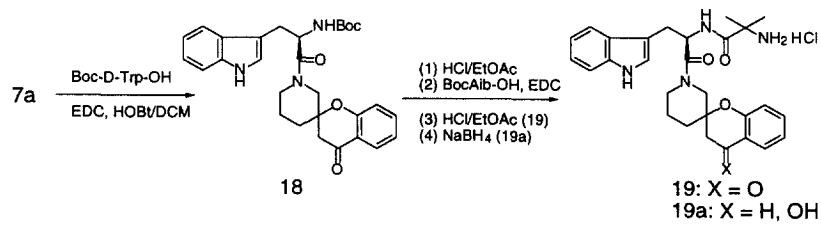
Scheme 4

Resolution of the racemic 4-oxo-spiro(3*H*-1-benzopyran-2,3'-piperidine) (**7a**) was accomplished by attaching (*R*)-(-)-*O*-acetylmandelic acid and separating the resulting two diastereomers (**17*R*** and **17*S***). The less polar one was crystallized and its absolute configuration was determined by single crystal X-ray analysis to be *RR*. Acidic removal of the chiral auxiliary followed by chromatographic purification gave both pure enatiomers **7*R*** and **7*S***.



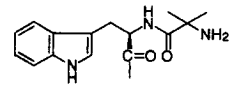
Scheme 5

Incorporation of the piperidines into the final secretagogues with a dipeptide cap was accomplished with standard peptide chemistry utilizing the Boc-protecting group. A typical procedure is shown in the following scheme with spiro(3*H*-1-benzopyran-2,3'-piperidine), Boc-D-Trp-OH and Boc-Aib-OH. Secretagogues bearing a hydroxy group (**19a**) were prepared by the direct reduction of the ketone (**19**) with sodium borohydride.



Scheme 6

Results and Discussion: Growth hormone release in vitro was determined in rat pituitary cell assays.[12] The Aib-D-Trp dipeptide was used for initial screening of the different piperidines since the SAR was well established in the L-162,752 series. Development of the lead compound initially was focused on the 4-position of the piperidine to study the effect of ring size and substitution pattern. The tetralin analog of L-162,752 (EC_{50} = 14 nM) was prepared to study the effect of indane ring expansion. Compound **20** (EC_{50} = 66 nM) was four times less potent than the parent L-162,752, which suggests that the expanded ring orients the benzene into a less optimal position. The spiro(indane-2,4'-piperidine) analogue **21** was more active than **20** but was still twofold less active than L-162,752. Addition of a ketone functionality had no effect on potency (compound **21a**), however, reduction to a hydroxy group (**21b** EC_{50}= 19 nM) appeared to increase the potency by twofold. On the other hand, introduction of a hydroxy or ketone moiety in the spiro(indane-1,4'-piperidine) series increased potency by ten fold. Clearly, this regioisomer does not offer any advantage over the spiroindane in L-162,752. To complete the SAR in the 4-spiropiperidine series, spiro(2*H*-1-benzopyran-2,4'-piperidine) was incorporated to give compounds **22**, **22a** and **22b**. The in vitro results were very similar to those of the compounds **21**, **21a**, and **21b**. These results suggest that the spiro(indene-1,4'-piperidine) provides a better conformation for receptor binding.



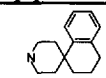
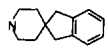
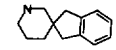
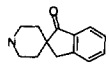
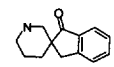
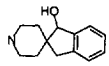
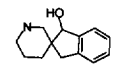
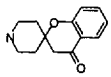
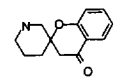
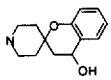
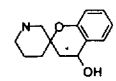
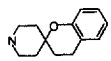
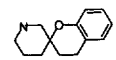
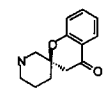
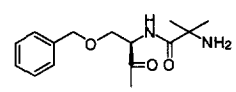
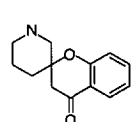
Entry	piperidine	EC_{50} (nM)	Entry	piperidine	EC_{50} (nM)
20		66	23		630
21		37	24		60
21a		42	24a		20
21b		19	24b		NA
22		37	19		1.8
22a		16	19a		1.2
22b		25	19b		2.9
19S		57	19R		1.2

Table 1

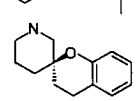
We then shifted our attention to the 3-spiropiperidine series. After much synthetic effort, the spiro(indane-1,3'-piperidine) incorporated secretagogue **23** was prepared, only to be found to be weakly active (EC_{50} = 630 nM). The results with its regioisomer **24** (EC_{50} = 60 nM) and its ketone analogue **24a** (EC_{50} = 20 nM) were much more encouraging. The activity breakthrough came when 4-oxo-spiro(3*H*-1-benzopyran-2,3'-piperidine) (**7a**) was incorporated. Compound **19** has an EC_{50} of 1.8 nM as a mixture of diastereomers in the rat pituitary assay. Again, reduction of the ketone to the hydroxy compound **19a** and complete reduction to **19b** only had marginal effects on in vitro potency. There is a profound effect of the stereochemistry at the spiro center, with *R* being almost 50 times more potent than *S*.





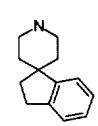
EC_{50} = 12 nM

25



EC_{50} = 3 nM

26



EC_{50} = 17 nM

L-162,970

Table 2

Substitution of the D-Trp with *O*-benzyl-D-Ser has been shown to improve oral activity in the 4-spiropiperidine series. The replacement slightly decreased potency of the 3-spiro series (Table 2). Compounds **25** and **26** were tested in vivo in beagles. The minimum effective dose that caused at least a

fourfold increase in serum GH levels was considered a positive response and was used to compare in vivo potencies. Both GHS **25** and **26** showed strong iv activity at 0.1 and 0.05 mpk, respectively, suggesting potent growth hormone release in vivo. Orally, compound **25** showed activity (1/2) at 0.5 mpk, while compound **26** gave a positive response (1/2) at doses as low as 0.25 mpk. For comparison, L-162,752 showed similar oral activity at a higher dose of 1 mpk, while MK-0677 is active at as low as 0.125 mpk.

The potent activity of both 4- and 3-spiro piperidine derived compounds with the same type of scaffold came as a surprise. In modeling them, the spiro groups in these compounds do not coincide assuming identical orientations of their dipeptide fragments. Thus, these secretagogues appear to express overlapping but not identical pharmacophores in their activation of the receptor. In this instance, as with many receptor antagonists, uniquely defined pharmacophores appear not to be required to express agonist activity.

In summary, systematic studies of different spiropiperidine systems have resulted in a novel 3-spiropiperidine series of potent growth hormone secretagogues. These compounds also demonstrated superior in vitro activity as compared to the lead compound L-162,752. Further modification of this lead and additional SAR studies will be reported in due course.

Acknowledgment: We would like to thank Amy Bernick for mass spectrometry support, Dr. Richard Ball for X-ray crystallography and Dr. Hal Selnick for helpful discussions.

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