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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF PHENYL PIPERAZINE- BASED PEPTIDOMIMETIC GROWTH HORMONE SECRETAGOGUES

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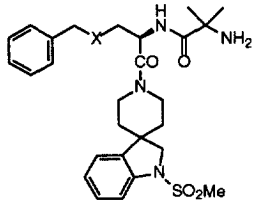
Abstract: A new class of potent, orally active phenyl piperazine-based GH secretagogues have been discovered from attempts to mimic the arrangement of the phenyl substitutent in the spiroindanyl piperidine and spiroindoline sulfonamide privileged structures of **4** and **1**, respectively. The best of these compounds, **18** (EC_{50} = 2.8 nM) is nearly as potent as MK-0677 for releasing GH from rat pituitary cells.

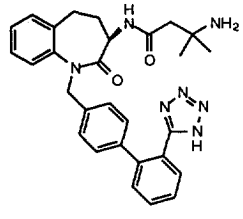
Numerous structurally distinct small molecule GH secretagogues have been reported in the literature within the past several years.[1] These include benzolactam secretagogues such as L-692,429 **3**[2] and the potent, orally bioavailable spiropiperidine-based growth hormone secretagogue MK-0677 **1**,[3] which is presently in clinical trials (see Figure 1).

Figure 1

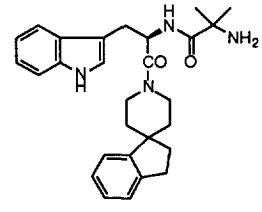


1, X = O, MK-0677

2, X = CH_2, L-163,255



3, L-692,429



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GH secretagogues such as MK-0677 are mechanistically indistinguishable from the peptidyl secretagogue GHRP-6[4] (**5**; His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2) and have been shown to amplify pulsatile GH secretion[5] by activating the recently identified GH secretagogue receptor (GHS-R).[6] It is anticipated that GH

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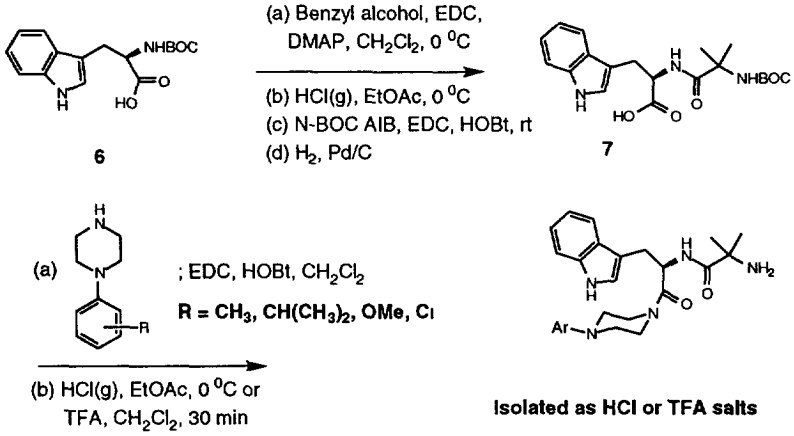
secretagogues may afford some of the beneficial physiological properties of GH such as growth stimulation, nitrogen retention, protein synthesis, lipolysis, bone elongation, and mineralization with lesser side effects than those associated with GH replacement therapy. In this paper, we report on the design and biological activities of phenyl piperazine-based GH secretagogues that evolved from our efforts to identify replacements for the spiroindanyl piperidine unit of **4** and the spiroindoline sulfonamide privileged structures of **1** (MK-0677) and **2** (L-163,255).

Chemistry

Phenyl piperazine-based GH secretagogues **8–11** were synthesized by a convergent synthetic route as shown in Scheme 1. In a 4-step sequence N-BOC-D-tryptophan **6** was converted to dipeptide acid **7** by protecting the acid functionality as its benzyl ester, removal of the BOC group with anhydrous hydrochloric acid in ethyl acetate, a standard peptide-type coupling of the amino intermediate with N-BOC-aminoisobutyric acid (N-BOC AIB) followed by hydrogenolysis of the benzyl ester with Pd/C gave acid intermediate **7**. Substituted phenyl piperazines were coupled with acid **7** by standard peptide-type coupling methods and the BOC unit was removed with either treatment with trifluoroacetic acid (TFA) in methylene chloride or with HCl (gas) in anhydrous EtOAc to afford secretagogues **8–11** as their TFA or HCl salts.

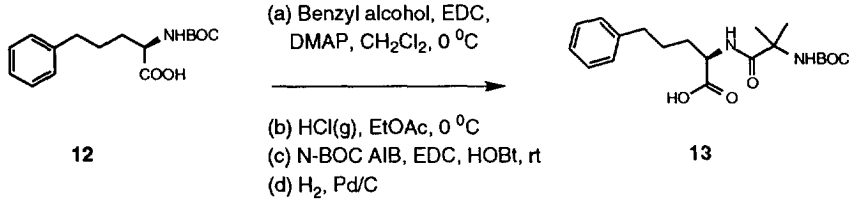
The synthesis of GH secretagogues **15** and **18–20**, in which a 3-phenylpropyl unit replaces the indol-3-yl substituent of secretagogues **8–11**, is described in Scheme 2 and Scheme 3. Dipeptide acid **13** was synthesized from N-BOC D-3-phenylpropylglycine **12** by taking advantage of synthetic methodology that was utilized for the preparation of **7**. Acid **13** was coupled with *o*-tolyl piperazine **14** (R = CH_3) by standard peptide coupling chemistry and the BOC protecting group was removed with TFA to provide **15** as its TFA salt. Phenyl piperazine secretagogues **18–20** that bear an *o*-sulfonamido substituent were prepared by first coupling acid **13** with *o*-nitro phenyl piperazine **16** (R = NO_2) and reducing the nitro functionality to afford the aniline derivative. Sulfonylation was accomplished by reacting this aniline with sulfonyl chlorides in the presence of triethylamine to afford the corresponding sulfonamide followed by BOC deprotection with strong anhydrous acid to afford **18–20**. Compound **21** was prepared from hydrolysis of the ester **20**.

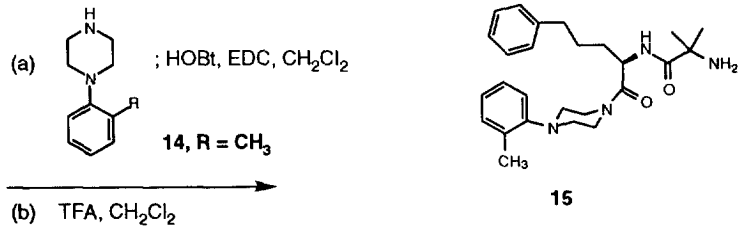
Scheme 1



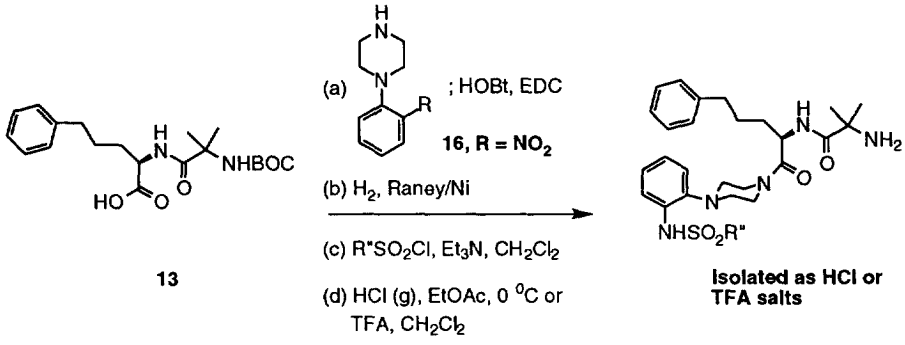
Ar			OMe	Cl
Compound	8	9	10	11

Scheme 2





Scheme 3



R"	CH_3	$CH(CH_3)_2$	CF_3	CH_2CO_2Me	CH_2CO_2H
Compound	17	18	19	20	21

Results and Discussion

Phenyl piperazine GH secretagogues **8–11** were designed as replacements for the spiroindanyl piperidine privileged structure of **4**[7] (Figure 2). GH secretagogue **4** was potent in vitro with an EC_{50} = 14 nM in the rat pituitary cell assay and orally active in dogs. Guided by the work on camphor-based GH secretagogues[8] and oxytocin antagonists[9] we reasoned that an *o*-tolyl piperazine may serve as a satisfactory replacement for the spiroindanyl pipepridine since the *ortho* methyl substituent on the phenyl unit of the *o*-tolyl piperazine would orient it orthogonal to the plane of the piperazine and thereby achieve the shape of the spiroindanyl piperidine (see Figure 2).

Figure 2

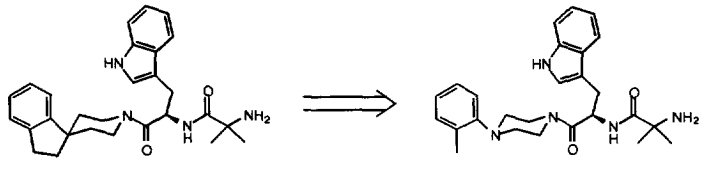
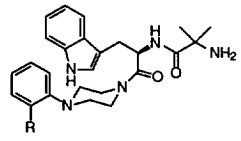


Table 1 shows the activities of D-Trp-based secretagogues **8–11**. *O*-Tolyl piperazine analog **8** was nearly tenfold less active than **4**. A larger isopropyl substituent at the *ortho* position of the phenyl group (**9**; EC_{50} = 210) was approximately as active as **8**. Surprisingly, use of a lipophilic chloro substitutent in place of the methyl unit of **8** led to a considerable loss in GH releasing activity in vitro (**11**; EC_{50} = 760 nM).

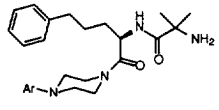
Table 1. D-Tryptophane analogs

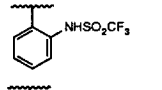
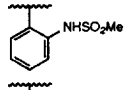
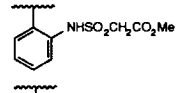
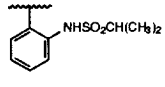
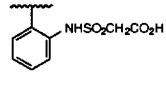


Compound	R	EC_{50} (nM)	Compound	R	EC_{50} (nM)
8	CH_3	150	10	OCH_3	490
9	$CH(CH_3)_2$	210	11	Cl	760

A key breakthrough in the genesis of MK-0677 was the discovery that polar substituents such as a methanesulfonamide at the C-1 position of the spiroindanyl piperidine led to a nearly tenfold increase in potency. Furthermore, use of an *O*-benzyl-D-serine or D-3-phenylpropylglycine in place of the D-Trp of **4** significantly improved oral activity in dogs.[7] Therefore, we decided to incorporate polar sulfonamides at the ortho position of the phenyl piperazine unit and substitute the D-Trp with a D-3-phenylpropylglycine. As shown in Table 2, a 3-phenylpropyl unit served as a satisfactory replacement for the indol-3-ylmethyl group of **8**. Like the MK-0677 series, incorporation of a methanesulfonamide group at the ortho position afforded a significant increase in intrinsic potency (**17**; EC_{50} = 6.3 nM).[10] Compound **17** was orally active in dogs for releasing GH after an oral dose of 1.0 mpk. Serum GH concentration rose from a basal level of 1.5 ng/mL to 125 ng/mL after 1 h and were down to 68 ng/mL at 2 h (last measured time point).

Table 2. D-Phenylpropylglycine analogs



Compound	Ar	EC_{50} (nM)	Compound	Ar	EC_{50} (nM)
15		100	19		200
17		6.3	20		4.5
18		2.8	21		2.3

Use of an isopropylsulfonamide increased the in vitro GH-releasing activity further (**18**; 2.8 nM). The intrinsic potency of **18** is comparable to the activity of MK-0677 (EC_{50} = 1.3 nM) in the rat pituitary cell assay. Incorporation of an ester or acid functionalities on the methanesulfonamide unit were also well tolerated as exemplified by **20** and **21**. But surprisingly, use of a trifluoromethanesulfonamide group (**19**; EC_{50} = 200 nM) led to a considerable loss in activity when compared with methanesulfonamide **17** (EC_{50} = 6.3 nM). The

nearly identical and excellent activities of **20** and **21** suggests that while the $NHSO_2$ group of **17–21** makes a key interaction with the receptor, the substituent on it may not be interacting with the receptor.

Summary

A new class of potent and orally active phenyl piperazine-based GH secretagogues, as exemplified by **17** (L-163,689; EC_{50} = 6.3 nM), has been discovered from attempts to mimic the arrangement of the phenyl substitutent in the spiroindanyl piperidine and spiroindoline sulfonamide privileged structures of **4** and **1**, respectively. Several of these compounds, including the isopropylsulfonamide **18** (EC_{50} = 2.8 nM) were found to be of similar potency to MK-0677 for releasing GH in the rat pituitary cell assay.[11]

Acknowledgments

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10. EC_{50} for half-maximal release of GH in the rat pituitary cell assay normalized for L-692,429 @ 60 nM.
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