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Substituted Bridged Phenyl Piperidines: Orally Active Growth Hormone Secretagogues

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Abstract—A new series of growth hormone secretagogues have been discovered. The best compound, **26j**, shows excellent ability to release growth hormone both in vitro and in vivo. The synthesis and biological activity of these compounds are discussed.

Small molecule growth hormone (GH) secretagogues have been extensively studied in the past several years. Research laboratories around the world have reported rather diverse structures that act similarly in both animal models and human to release growth hormone.[1] From Merck Research Laboratories several classes of highly active small molecule GH secretagogues have been reported. They include the biphenyl benzolactams, such as **1**;[2] azaspiroindanes, represented by **2**;[3] spiroindanes, like **3**;[4] 3,3-disubstituted piperidine class, like **4**;[5] and substituted phenyl piperazine series, compound **5**[6] (Fig. 1). In this communication, we report a new series of the substituted phenyl tropane containing secretagogues in which the best compound displays excellent in vitro activity and very good oral activity in beagles.

The synthesis of the non-substituted phenyl intermediate **10** started from the commercially available tropinone **6**. Treatment of **6** with phenyllithium gave hydroxy tropane **7** in 24% yield. Acidic dehydration of **7** afforded alkene **8** quantitatively.

Hydrogenation of **8** using Pd on carbon as catalyst in EtOH at 1 atm provided **9** in excellent yield. Demethylation was accomplished in 95% yield by treatment of **9** with α-chloroethylchloroformate under reflux in dichloroethane, followed by refluxing in MeOH. The hydrochloride salt **10** was then coupled with different amino acid blocks to provide the intermediates which were deprotected to give final products (Scheme 4). The synthesis is outlined in Scheme 1.

Exploration of substitutions at the phenyl *ortho* position was also carried out based on the results from studies of compounds **2**, **3**, and **5**. The preparations of these *ortho*-substituted intermediates are slightly different from the above synthesis and they are described in Schemes 2 and 3.

Tropinone **6** was treated with $KN(TMS)_2$ in THF at −78 °C, followed by traping with *N*-phenyl trifluoromethanesulfonimide to give **14** in 75% yield. Compound **14** was mixed with 2-MePhMgBr, CuI in THF at 0 °C to afford **15** in 94% yield. Reduction of **15** with Na/NH_3 in THF at −78 °C provided **16** in 82% yield. Demethylation gave a hydrochloride salt of *ortho*-methyl substituted phenyl intermediate **17** (Scheme 2). To prepare ester **22**, the demethylation of **6** was carried out first under the conditions described earlier. The nitrogen atom was then protected with Boc_2O to give **18** in 79% yield.

Compound **18** was converted to vinyl triflate **19** (92%) and vinyl tin **20** (72%). Stille coupling of **20** with ethyl 2-bromobenzoate afforded **21** in 42% yield. Hydrogenation of

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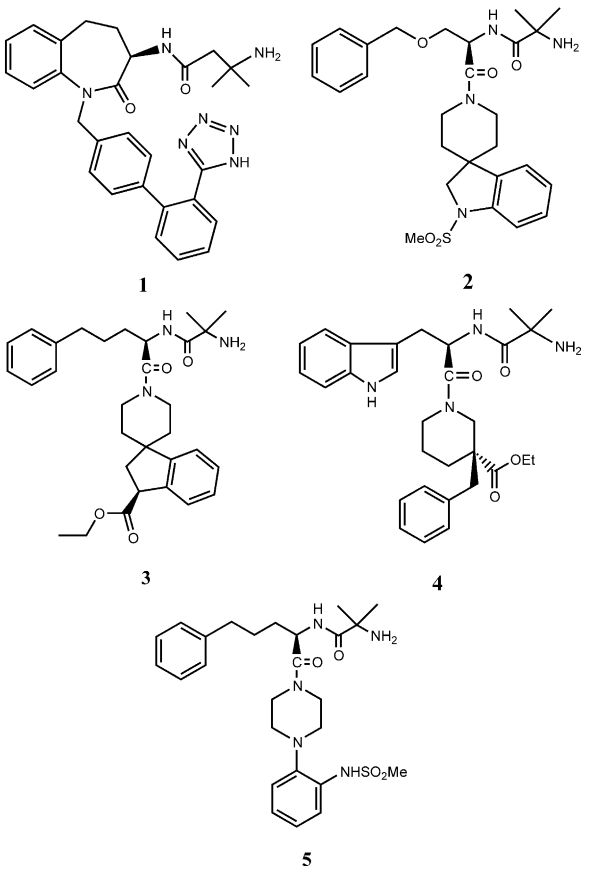
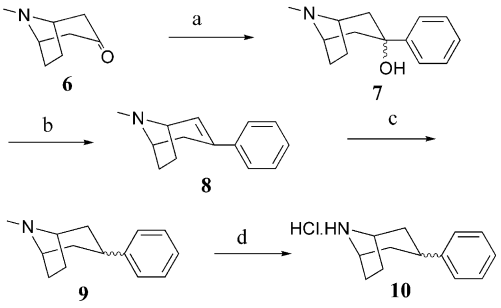
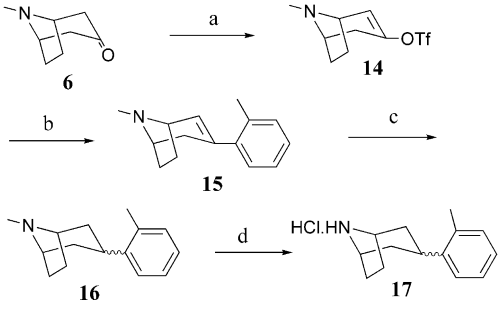


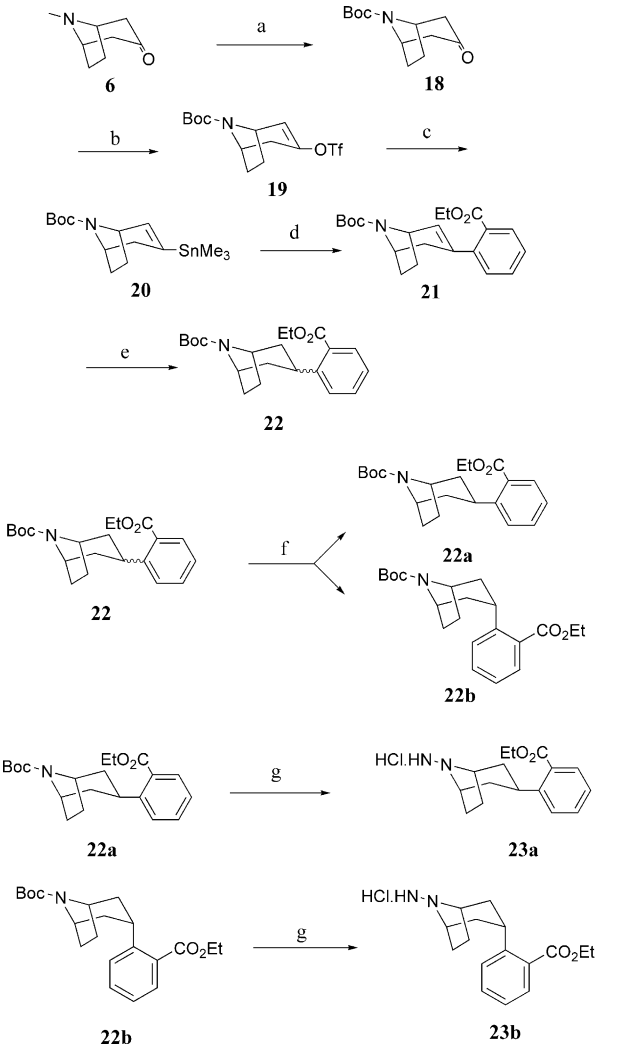
Figure 1. Some highly active GH secretagogues.



Scheme 1. (a) PhLi, ether, 0 °C→rt, 24%; (b) 48% HBr, 75 °C, 100%; (c) H_2, Pd/C, EtOH, 96%; (d) α-chloroethyl chloroformate, dichloroethane, reflux; MeOH, reflux, 95%.



Scheme 2. (a) $KN(TMS)_2$, THF, −78 °C; $(CF_3–SO_2)_2NPh$, −78 °C, 75%; (b) 2-MePhMgBr, CuI, THF, 0 °C, 94%; (c) Na/NH_3, THF, −78 °C, 82%; (d) α-chloroethyl chloroformate, dichloroethane, reflux; MeOH, reflux.

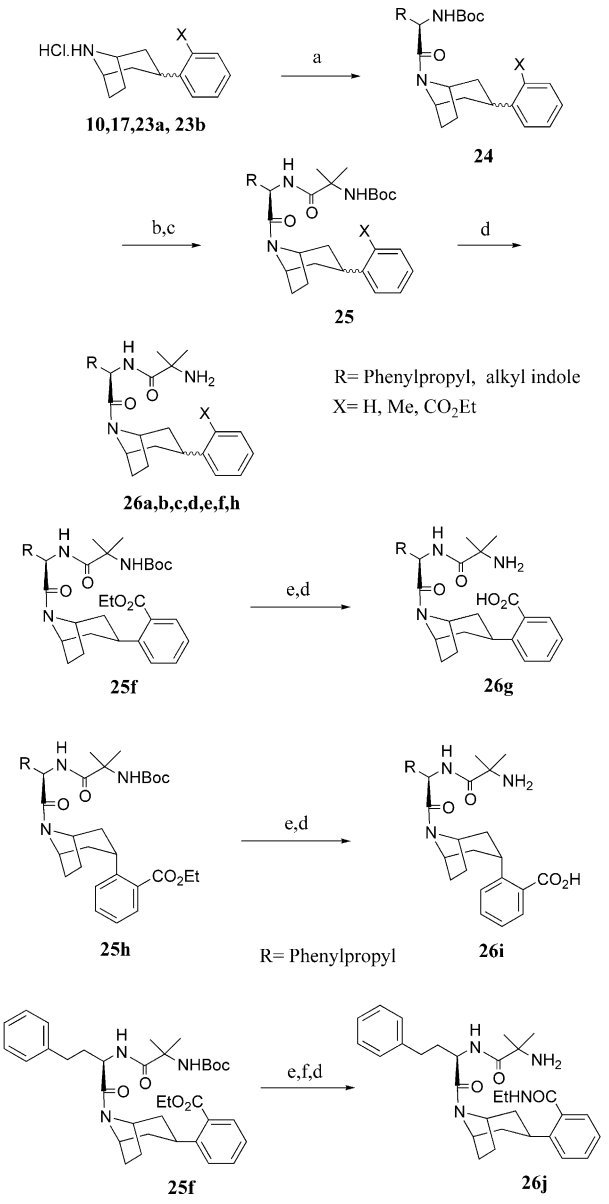


Scheme 3. (a) α-Chloroethyl chloroformate, dichloroethane, reflux; MeOH, reflux; Boc_2O, NaOH, *i*-PrOH, rt, 79%; (b) $KN(TMS)_2$, THF, −78 °C; $(CF_3–SO_2)_2NPh$, −78 °C, 92%; (c) $(Me_3Sn)_2$, LiCl, $(Ph_3P)_4Pd$, THF, reflux, 72%; (d) 2-$BrPhCO_2Et$, $(Ph_3P)_4Pd$, toluene, reflux, 42%; (e) Pd/C, H_2, MeOH, 97%; (f) recrystallization from hexane/EtOAc at 0 °C (g) HCl/dioxane, 100%.

21 gave a 1:1 mixture of **22** (97%) which was separated to isomer **22a** and **22b** via flash column and recrystallization[7] (Scheme 3). The crystal structure of **22a** was determined by X-ray crystallography. **22a** and **22b** were deprotected using HCl in dioxane to give **23a** and **23b** quantitatively.

Conversion of intermediates **10**, **17**, **23a**, and **23b** into the final secretagogues was accomplished via standard peptide coupling/deprotection reactions as shown in Scheme 4. The acids were prepared in one additional step by basic hydrolysis of esters, and the amide was made by EDC coupling of ethyl amine with the corresponding acid.

All the compounds were evaluated for their ability to release growth hormone in the rat pituitary cell assay.[8] Methyl substituted and non-substituted phenyl amines **10** and **17** were used as a 1:1 mixture of *cis*/*trans* isomers. Each of these compounds (**26a–d**) were moderately potent. Separation of the *cis* and *trans* isomers of

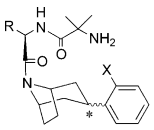


Scheme 4. (a) Amino acid, EDC, HOBT, 4-methyl morpholine, rt, 50–90%; (b) HCl in EtOAc, rt, 100%; (c) BocNHC(Me)$_2$COOH, EDC, HOBT, 4-methyl morpholine, CH_2Cl_2, rt, 50–85%; (d) HCl in dioxane, rt, 60–80%; (e) NaOH/MeOH/H_2O, 96%; (f) $EtNH_2$, EDC, HOBT, *N*-methylmorpholine, CH_2Cl_2, 71%.

26e showed that the *cis* isomer was more potent. For example, the *cis* isomer of ester **26f** is 6-fold more potent than the *trans* isomer **26h**, while the corresponding acid **26g** is 50 times better than **26i**. The ethyl amide **26j** shows an excellent ability to release growth hormone (**26j** EC_{50} = 1.3 nM vs **2** EC_{50} = 1.0 nM). Potent GH secretagogues have been also generated in related but different structural classes when the ethyl amide moiety was introduced to the 2-position of the phenyl ring.[1,2] Table 1 summarizes the findings.

26j was evaluated for its GH releasing ability in the beagle dog model. It was orally active in dogs at 0.25 mg/kg for releasing GH after oral administration. Serum GH concentration rose from a basal level of 1.7–55 ng/mL at 30 min and returned to the baseline after 3 h. The in vivo data was comparable to that of compound **2**.

Table 1. SAR of bridged substituted phenyl piperidines and A comparison to compound **2**



Compd **26**	R	X	*	EC_{50} (nM)
a	Phenylpropyl	H	*cis* + *trans*	24
b	3-Indolylmethyl	H	*cis* + *trans*	62.8
c	Phenylpropyl	Me	*cis* + *trans*	78.4
d	3-Indolylmetyhyl	Me	*cis* + *trans*	33.2
e	Phenylpropyl	CO_2Et	*cis* + *trans*	90
f	Phenylpropyl	CO_2Et	*cis*	48
g	Phenylpropyl	CO_2H	*cis*	9.6
h	Phenylpropyl	CO_2Et	*trans*	324
i	Phenylpropyl	CO_2H	*trans*	> 500
j	Phenylpropyl	CONHEt	*cis*	1.3
2				1.0

Data from the rat pituitary cell assay. The results are from a single experiment. All EC_{50} are normalized against standards, compound **1** (EC_{50} = 60 nM).

In summary, a new class of potent bridged substituted phenyl-piperidine GH secretagogues has been reported. The best compound, **26j**, is not only highly potent in the rat pituitary cell assay but also orally active at low dose in dogs to release growth hormone.

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7. For resolution of **22a** and **22b** by flash column and recrystallization: A solution of compound **21** (0.67 g, 1.87 mmol) in MeOH (20 mL) was charged with 10% Pd/C and hydrogen at 1 atm for 20 h. The mixture was filtered through Celite to give **22** as a colorless oil (0.65 g, 97%) after removal of the solvent. A flash column was carried out using 1:9 EtOAc/hexane as the elute to give 0.184 g of **22a** (faster component), 0.047 g of **22b** (slower component) and 0.35 g of the mixture. More **22a** (0.1 g) was obtained by recrystallization in hexane/EtOAc at 0 °C and using **22a** as a seed crystal. The mother liquid was then subjected to a second flash column (1:9 EtOAc/hexane) to isolate pure **22b** (0.17 g). ^{1}H NMR (400 MHz, $CDCl_3$): **22a** 7.74 (d, $J=7.94$ Hz, 1H), 7.40 (t, $J=7.94$ Hz, 1H), 7.31 (d, $J=7.77$ Hz, 1H), 7.22 (t, $J=7.77$ Hz, 1H), 4.35 (m, 2H), 4.22 (m, 2H), 4.08 (m, 1H), 2.50 (m, 2H), 2.00 (m, 2H), 1.80 (m, 2H), 1.70 (m, 2H), 1.50 (s, 9H), 1.35 (t, $J=7.1$ Hz, 3H); **22b** 7.60 (d, $J=7.94$ Hz, 1H), 7.38 (t, $J=7.93$ Hz, 1H), 7.31 (d, $J=7.7$ Hz, 1H), 7.18 (t, $J=7.7$ Hz, 1H), 4.32 (m, 2H), 4.22 (m, 2H), 3.25 (m, 1H), 2.50 (m, 2H), 2.06 (m, 2H), 1.62 (m, 2H), 1.48 (s, 9H), 1.35 (t, $J=7.1$ Hz, 3H), 1.28 (m, 2H).

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