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NAPHTHO-FUSED AZEPINES AS POTENT GROWTH HORMONE SECRETAGOGUES

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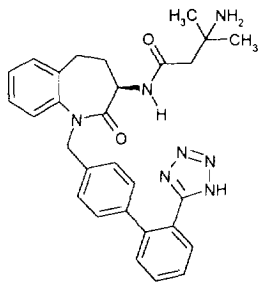
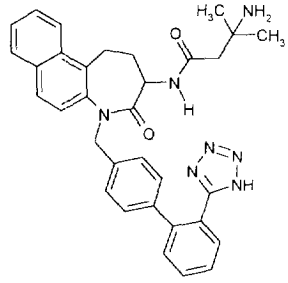
Abstract: Computerguided improvements of known growth hormone secretagogues are reported. These are a new series of napthofused azepines. Structure-activity relationships are different than in the corresponding benzo-fused azepines. © 1997 Elsevier Science Ltd.



L-692,429

(1)



NNC-26-0610

(2)

Introduction: Several groups have entered the fascinating field of growth hormone secretagogues[1] within recent years. These efforts have followed in the foot steps of more and more studies pointing to interesting clinical applications of human growth hormone (hGH). Human GH has been used in the treatment of growth retarded children for decades. However, with the introduction of recombinant hGH, unlimited supplies are now available for clinical applications of rhGH, other than the classical indications. Human GH has for example been shown effective in the treatment of burns, in patients with Turners syndrome, to reverse catabolic conditions and in reducing some of the effects of age[1k]. Instead of direct hGH replacement therapy it appears attractive to use hGH-secretagogues because most cases of human GH deficiency result from GH-secretory defects rather than a deficit in pituitary GH-production thus allowing an oral route of administation if a suitable small-molecule secretagogue can be found. Such therapy would probably also allow control of GH in a manner that mimics the natural pulsatile release of GH more closely than direct GH-therapy. The endogenous GH-secretagouge (growth hormone releasing hormone, GHRH) is a large peptide and its receptor has been isolated[1i]. However, short peptides (GHRP's) that release GH are known[1d], but their actions are mediated by another receptor[1c]. The prototype GHRP-6 is a hexapeptide[1d] with the amino acid sequence His-D-Trp-Ala-Trp-D-Phe-Lys-

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NH_2. Early in our program, we discovered a number of shorter peptides with approximately the same potency. With the aid of molecular modelling we have established a common model of the pharmacophoric elements in two of these peptides and another known secretagogue[1b] (**1**) (L-692,429; Merck). Guided by modelling we have been able to improve the potency of (**1**) with a factor of 10, measured in a rat pituitary assay, by fusing a benzene ring onto (**1**) as in the napthoanalog (**2**) NNC 26-0610.

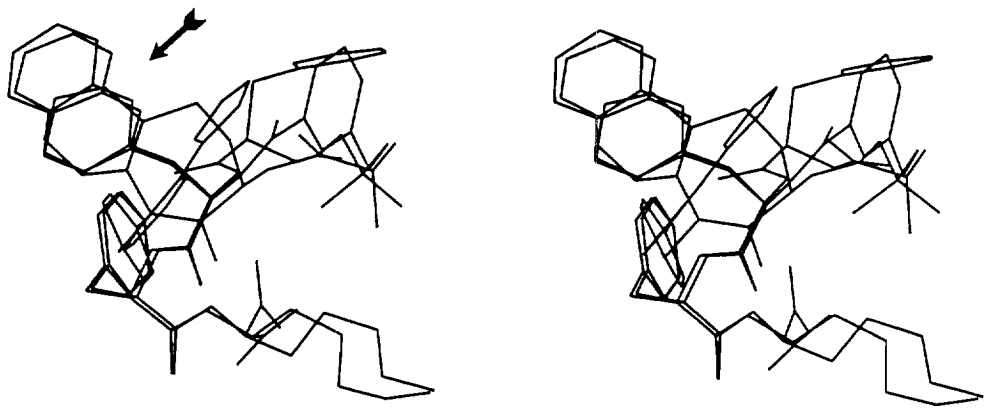
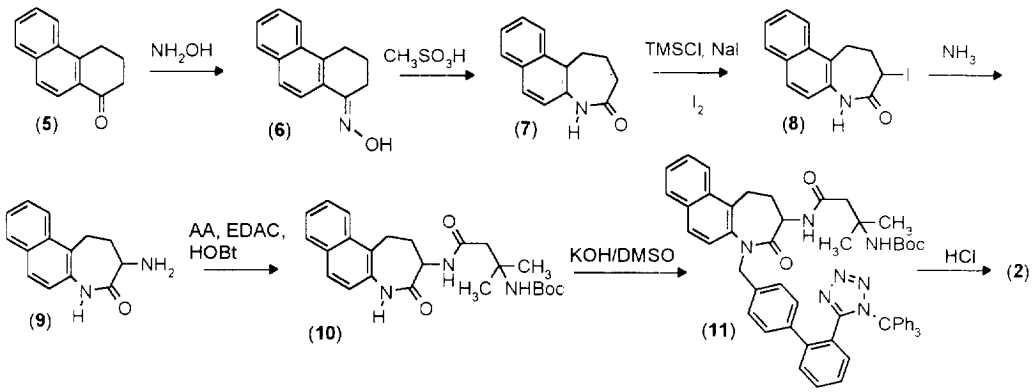


*Fig. 1. Stereoview of superposition of (**1**), (**3**) and (**4**). "Missing" pharmacophore of (**1**) indicated by arrow*

Modelling: GHRP-6 and (**1**) appears to bind to the same receptor but with different activity. GHRP-6 is approximately 10 times as potent as (**1**). One possible explanation for the increased activity is that GHRP-6 cortains an additional binding element which is not present in (**1**). This additional pharmacophore could possibly be identified by superposition of GHRP-6 with (**1**). In the superposition previously reported by Schoen et al[1b] the amino group, the benzolactam ring and the terminal ring of the biphenyl of (**1**) aligns fairly well with the N-terminus, the D-Trp residue and the D-Phe residue in GHRP-6. We did a similar superposition using distance geometry calculations (DGEOM95[3]) but replacing the highly flexible GHRP-6 with the two potent and shorter GHRP-6 analogues (**3**) NNC 26-0079 (Ala-Phe-D-2-Nal-D-Phe-Lys-NH_2; EC_{50} = 2 nM in a rat pituitary assay) and (**4**) NNC 26-0140 ((3-aminomethylbenzoyl)-D-2-Nal-D-Phe-Lys-NH_2; EC_{50} = 7 nM). Compared to the superposition suggested by Schoen[1b] the only major difference was that the aromatic ring of D-Phe was mapped upon the "inner" phenylene (closer to the azepinone) in (**1**). This difference was based on the observed loss in potency by sequential removal of increasing parts of the biphenyltetrazole moiety of (**2**), where removal of the "inner" phenylene leads to greater reduction in potency than what was observed by removal of either the "outer" phenylene or the tetrazole ring (Table 1). The resulting molecular superpositions were energy optimized by a SYBYL multifit[3] approach. Our model (figure 1) suggested that fusion (indicated by an arrow in fig 1) of an additional aromatic ring to the ben-

zazepinone might add an additional binding element to (**1**). Indeed, this compound, (**2**) turned out to be more than ten times as potent as (**1**) (Table 1).



Synthesis: The synthesis of (**2**) was achieved by a 7-step sequence utilising tetrahydrophenantrenone (**5**) as starting material. This was converted in quantitative yield to the napthoazepinone (**7**) from its oxime (**6**). For introduction of a leaving group in the 3-position we used the method by King et al[4] using trimethylsilyl chloride, sodium iodide and iodine leading to iodide (**8**) in moderate to good yield. Iodine was substituted by ammonia (methanol, 100°C in a Parr-apparatus) to give (**9**) in good yield. An alternative, but longer route to (**9**) involved the dichlorination of (**7**) with PCl_5, reduction to the monochloro-analog, substitution by azide and reduction to amine (**9**).

	Y	X						
naphtho series	(**2**): 4 nM	nd	(**18**): 8500 nM	nd	(**19**): 37 nM	(**20**): 175 nM	nd	
benzo series	(**1**) 125 nM	(**21**) 1700	(**22**): 1000 nM	(**23**) inactive	(**24**): 62 nM	nd	(**25**) 30 nM	

Table 1. Potency data. Rat pituitary cell assay. Data are ED_{50} values and based on the assumption that one enatiomer is inactive.

Using N-Boc-3-methyl-3-aminobutanoic acid and traditional acylation conditions (EDAC, HOBt) we got to (**10**) in good yield. Finally alkylation (DMSO, KOH) with a suitable benzylic bromide and deprotection with acid (HCl in EtOAc) gave the desired compound (**2**) (NNC-26-0610). It was possible to separate the enantiomers (recrystallisation of the tatrate salts of (**9**)) but in general we used the racemic material. Using the same methodology we prepared the compounds which are summarised in table 1.

Results and discussion. The tabular overview[5] in table 1 shows that the napthofused derivatives have a different SAR compared to the corresponding benzofused derivatives. Although the derivative (**2**) was more than one order of magnitude better than its benzo-analogue (**1**) the situation was reversed in the case of the benzyl substituted analogues (**18**) and (**22**), in which case napthofusion was a clear disadvantage. Naphofusion was also a disadvantage when we shortened the attached aminoacid side chain as in compound (**20**).

We observed a low oral bioavailability (<5% in rats) of compound (**2**) and speculated that removal of the acidic and relatively polar tetrazole-ring could be of help. To test this hypothesis we prepared the derivative (**19**). However the oral bioavailability of (**19**) remained low as in the tetrazole analogues and the increase in potency by napthoannelation was smaller than in compound (**2**). Nevertheless, it is of interest that an oxadiazole moiety readily functions as a bioisostere for a tetrazole in this type of compounds.

Notes and References

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5) The biological set-up is described in detail in reference (1g).

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