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New Growth Hormone Secretagogues: *C*-Terminal Modified Sulfonamide-Analogues of NN703

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Abstract: The *C*-terminal the orally active growth hormone secretagogue **NN703** was changed to prepare analogues with inverse sulfonamides and inverse amides. The compounds showed high activity in a *in vitro* rat pituitary model.

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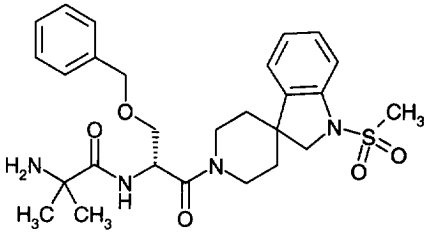
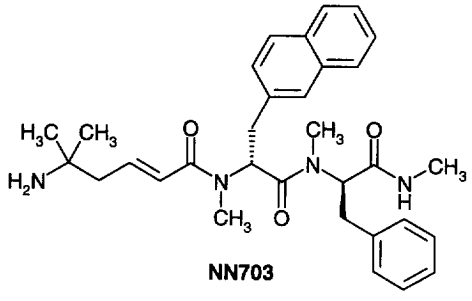
Introduction: The field of growth hormone secretagogues is currently an exciting and fast evolving area in medicinal chemistry.[1)] The success of the first hexapeptides GHRP-6 and GHRP-2 triggered a number of research programs, that resulted in orally available compounds, from which the clinical candidates **MK-0677**[2)] and **NN703**[3)] are the most prominent examples. By the structure of **MK-0677**, we were inspired to synthesize a number of **NN703**-analogues which are modified at the *C*-terminal. An inverse peptide structure at the *C*-terminal of **NN703**-analogues would give an easy access not only to inverse amides but also to sulfonamides. Especially sulfonamide-moieties seemed to be of interest, since this moiety seems to be important for the high activity of **MK-0677**.[4)]



MK-0677



NN703

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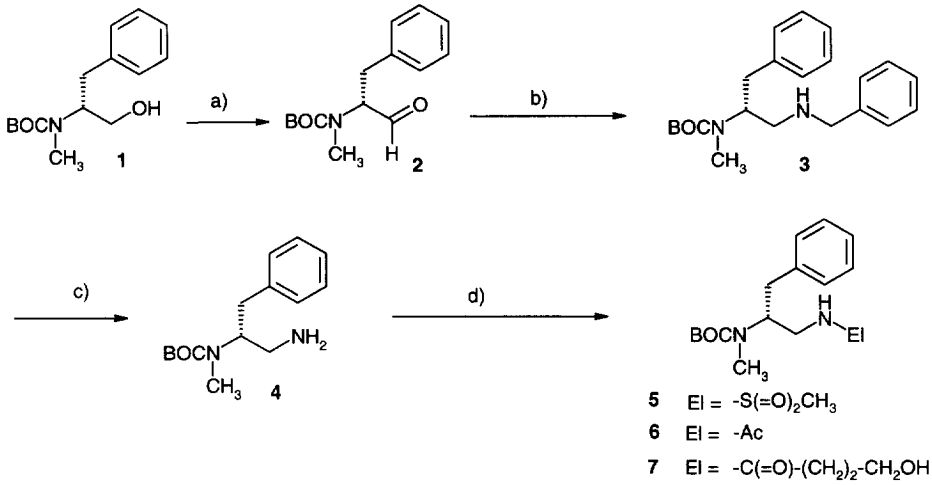
PII: S0960-894X(99)00167-5

Discussion: We anticipated to use mono-protected diamines of type **4** as starting materials for the *C*-terminal-modified growth hormone secretagogues.

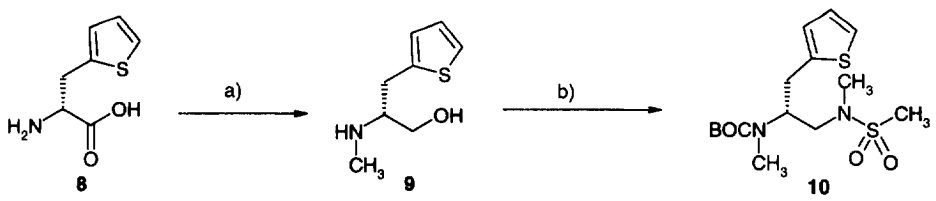
Since a mesylation of **1** resulted in our hands in immediate cyclization, we chose to oxidize **1**[5,6] with sulfur trioxide pyridine complex[7] to the corresponding aldehyde **2**. A reductive amination with benzylamine afforded **3**. After debenzylation, the desired mono-*N*-protected diamine **4** was obtained.

The amide **4** was reacted with different electrophiles, such as methanesulfonic acid chloride or acetic anhydride yielding **5** and **6**. When succinic anhydride was used as electrophile, the resulting acid was subsequently reduced with lithium borohydride to alcohol **7**.



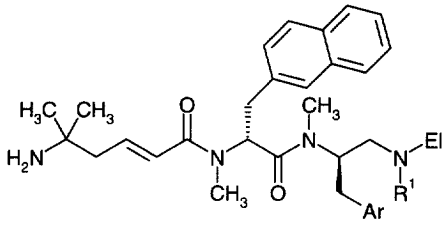
a) $SO_3 \cdot$ py, NEt_3; b) $PhCH_2NH_2$, $NaCNBH_3$, HOAc; c) H_2, $Pd(OH)_2$; d) CH_3SO_2Cl, NEt_3, CH_2Cl_2, -78 °C; or Ac_2O; or i succinic anhydride ii ClC(=O)OEt, NEt_3 iii $LiBH_4$

Similarly, the thiophene analogue **10** was synthesized form D-(2-thienyl)alanine (**8**). Formylation, reduction to alcohol **9**, Swern oxidation, and reductive amination furnished an amine, which was transferred into the sulfonamide **10**.



a) i HCOOH, Ac_2O ii $NaBH_4/I_2$; b) i $(BOC)_2O$, NaOH ii $(COCl)_2$, DMSO, NEt_3 iii NH_2CH_3, $NaCNBH_3$, HOAc iv $CH_3(S=O)_2Cl$, NEt_3 -78 °C

The growth hormone secretagogues **11**, **12**, **13**, and **14** were obtained by deprotection of the BOC-protected amino-group with trifluoroacetic acid. The peptide couplings were performed with N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDAC)/ 1-hydroxy-7-azabenzotriazole (HOAt)[8] and BOC-protected *N*-methyl-2-naphthylalanine[3] and 5-(*tert*-butoxycarbonylamino)-5-methylhex-2-enoic acid.[3] The BOC-groups were removed with 50% trifluoroacetic acid in dichloromethane at 0 °C.



El	Ar	R^1	
$-S(=O)_2CH_3$	phenyl	H	**11**
-Ac	phenyl	H	**12**
$-C(=O)-(CH_2)_2-CH_2OH$	phenyl	H	**13**
$-S(=O)_2CH_3$	2-thienyl	CH_3	**14**

Compounds **11**, **12**, **13**, and **14** were tested in a *in vitro* rat pituitary assay.[9] The results are shown in Table 1.

Table 1

In-vitro screening

Entry	**NN703**	**11**	**12**	**13**	**14**
EC_{50} [nM]	2.7	2.5	25.0	34.0	3.0

As it can be seen from the test results, an inverse structure at the *C*-terminal of analogues of **NN703** is similarly active on a rat pituitary as the amide with peptide orientation. Especially, compounds with sulfonamides at the *C*-terminal show high growth hormone secretagogue activity. An amide substructure, which is inverse orientated, when compared to a peptide, seem to result in a compound with slightly decreased activity.

Conclusion: A new type of *C*-terminal motif was introduced to analogues of **NN703**. The introduction of inverse peptide bonds gave compounds with slightly lower activity, when compared **NN703**. A sulfonamide moiety, however, seems to be very suitable for achieving high potency as it can be seen from examples **11** and **14**.

Notes and References

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