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SYNTHESIS OF AZAPEPTIDES FROM HINDERED AMINES LEADING TO NOVEL GROWTH HORMONE SECRETAGOGUES

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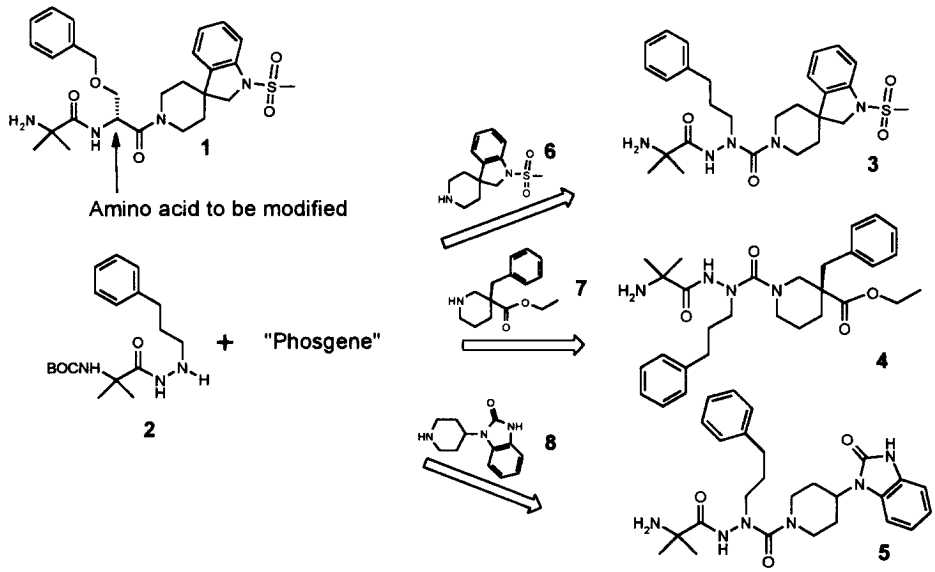
Abstract: Preparations of aza analogues of known potent growth hormone secretagogues (GHS) were unsuccessful using known methods for preparation of azapeptides when hindered amines were employed. We now report a coupling method using bispentafluorophenylcarbonate as a "balanced reactivity" phosgene equivalent to solve these problems.

During our ongoing program directed at finding new and improved growth hormone secretagogues[1] we became interested in preparing azapeptide[2] analogs of known GHSs such as MK677 (**1**) as the interest in such compounds continues to expand. There is a plethora of possible indications for such compounds including treatment of burns, for Turners syndrome, for sleep enhancement, to reverse catabolic conditions and in reducing some of the effects of age.[1] All known GH-secretagogues contain one or more chiral, nonbiogenic D-amino acids that makes the synthesis of such compounds more expensive and lengthy. Azapeptides in contrast, are achiral and reported to be easy to synthesize[2] and to offer a good chance of retaining the biological activity of the parent peptide.



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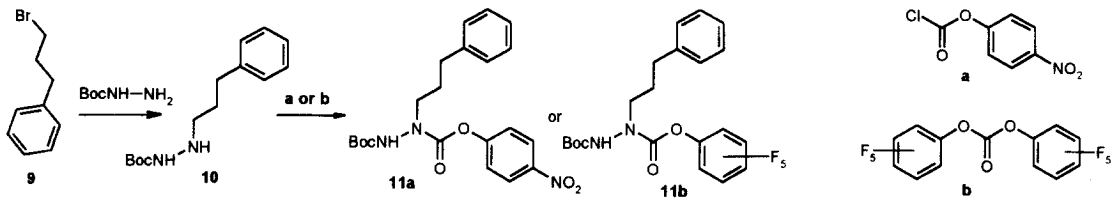
Based on precedent in the literature[2] it appeared to be a relatively simple task to prepare compounds such as **3** and **4** (close or direct aza-analogs of known GHSs) and **5** (novel type) from a substituted hydrazine such as **2**, an amine such as **6,7** or **8** and phosgene or a phosgene equivalent. However, we quickly learned that activation at the dipeptide level was troublesome and resorted to Boc-hydrazine as the starting material. Direct alkylation with 3-bromopropylbenzene (**9**) to give **10** worked well (85% using a 2 fold excess of Boc-hydrazine) and was, in our hands, superior to reductive alkylation.[3] Reaction with 4-nitrophenyl chloroformate produced crystalline **11a** in 95% yield.



This material reacted with primary amines but not with secondary amines or piperidines (like **6-8**) and there were in fact hardly any references to such transformations in the literature.[4] As we took this to be a reactivity problem we investigated phosgene, triphosgene and carbonyldiimidazole as *in situ* coupling agents with a number of variations in temperature, solvent and order of addition but with no success.[3] Apparently, these reactants are too reactive and cause polymerizations.[2] Looking for "intermediate reactivity" agents we tried bis(pentafluorophenyl)carbonate[3] and obtained stable crystalline **11b** with no signs of urea formation. Using this reagent in DMF (DCM did not work) we were able to carry out the desired couplings in moderate to good yields (50-60%). The subsequent steps (deprotection with TFA, EDAC/HOAt mediated coupling of BocAib followed by a final deprotection with TFA) were trivial and produced the desired compounds **3, 4** and **5** in good yields. We believe that this method can be extended to many other hindered amines and expand the scope of azapeptides significantly. The biological potencies of **3, 4** and **5** were measured in a rat pituitary cell assay and we observed EC_{50} of 14nM, 1175nM and 15nM indicating that **3** is about ten times less potent than **1** but **3** is still a very potent compound whereas **4** has lost a potency factor of 1000. For compound **5** no reference compound has been made.

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Notes and References

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2 Gante, J., *Synthesis*, **1989**, 405-413

3 Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539-44

4 For proline as an exception see Andre, F.; Marraud, M.; Boussard, G. *Tetrahedron. Lett.* **1996**, *37*, 183-186.