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Solid phase Synthesis of peptoid derivatives containing a free C-terminal carboxylate

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Abstract: The use of the 2-chlorotritylchloride resin gives access to the solid-phase synthesis of peptoid derivative C-terminal acid with a good yield by hindering the formation of diketopiperazine. This solid support was used in the synthesis of a new series of peptoid inhibitors of zinc metallopeptidases.

Peptoids are synthetic oligomers of N-substituted glycines [1]. However only peptoid C-terminal amides have so far been synthesized. Indeed, the solid phase synthesis of a peptoid C-terminal acid requires a C-terminal ester linking the growing peptoid chain to the resin. A diketopiperazine formation is generally found at the level of the dipeptoid preventing thus the chain extension [2]. Nevertheless, as their parent peptide, the biological activity of peptoids is expected to depend on their C-terminal functions, and free C-terminal carboxylic acids could be essential for their activity. Thus, for instance, the design of pseudo-peptides inhibitors of zinc metalloproteases endowed with a carboxy- or a dipeptidyl-carboxypeptidase activity was shown to require a free carboxylate group in C-terminal position [3,4]. The preparation of their peptoids analogs will therefore request a C-terminal acid function.

The 2-chlorotritylchloride resin [5] has been recently shown to avoid diketopiperazine formation in peptides bearing a glycine or a proline at their C-terminus [6]. This has been mainly attributed to the steric hindrance of the trityl group preventing cyclization at the dipeptide level. With the aim of preventing such side reaction in peptoids, this resin was used in the synthesis of the dipeptoid model Nphe-Nleu **1** and the results compared to those obtained with the classical HMP resin [7]. The solid phase synthesis of peptoids is straightforward especially by using alternative coupling of bromoacetic acid and nucleophilic substitution of the bromine atom by different amines [8,9]. This synthetic pathway was thus followed for the chain elongation on both resins after the loading of bromoacetic acid on Wang/HMP resin with diisopropylcarbodiimide (DIC) and on 2-chlorotritylchloride resin with diisopropylethylamine (DIEA). When using the HMP resin, no dipeptoid **1** was obtained after cleavage by a trifluoroacetic acid (TFA)/water mixture (95/5, v/v). HPLC analyses of the reaction mixture at the step of introduction of benzylamine demonstrated the quantitative formation of the corresponding diketopiperazine **2**. Conversely, when the 2-chlorotritylchloride resin was used, a 78 % yield in **1** was obtained after cleavage by a TFA/water mixture (95/5, v/v). The by-product generated at the step of introduction of benzylamine was characterized as **2** by HPLC analysis.

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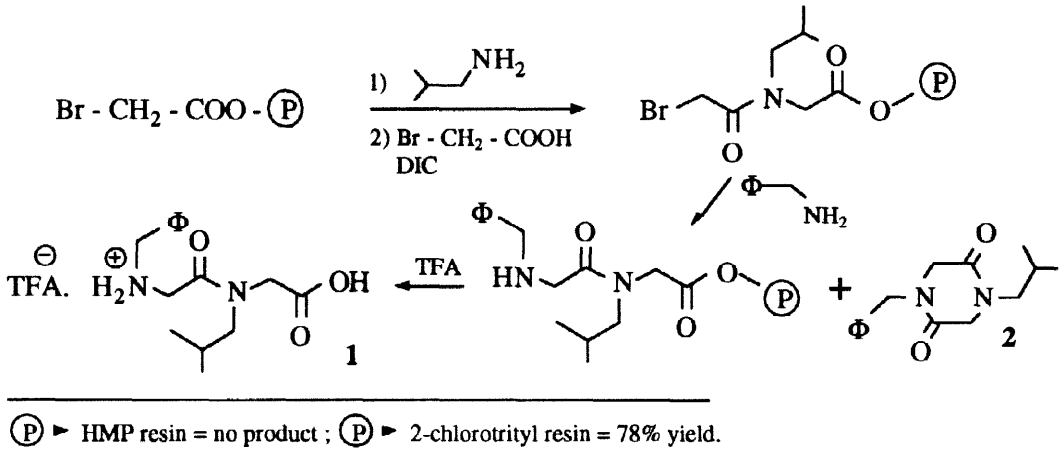
Figure 1



Synthetic route used for the synthesis of the dipeptoid model H-NPhe-NLeu-OH **1** on 2-chlorotritylchloride resin or Wang/HMP resin. The diketopiperazine **2** corresponds to the by-product observed in this synthesis.

The amount of diketopiperazide formed seems to be independent on the nature of the amine introduced on the C-terminal glycine. This method was used to investigate the recognition of thermolysin, a bacterial zinc metallopeptidase which is currently used as a model of physiologically important enzymes such as angiotensin converting enzyme (ACE) and neprilysin (NEP) or endothelin converting enzyme (ECE) for the design of inhibitors. For this purpose, an additional coupling step of bromoacetic acid and a subsequent substitution of the bromine atom by potassium thioacetate was achieved on the peptoid H-N-Phe-Gly-OH loaded on the 2-chlorotrityl chloride resin. After cleavage from the resin by a TFA/water mixture (95/5, v/v) and a final deprotection of the acetyl group by NaOH 1N, the compound, HS-CH_2-CON($CH_2\Phi$)-CH_2-CONH-CH_2-COOH, was obtained. The inhibitory potency (Ki = 15 μM) of this compound to inhibit TLN was found only 8 times lower than that of the corresponding peptide, HS-CH_2-CH($CH_2\Phi$)-CONH-CH_2-COOH (Ki = 1.8 μM).

In conclusion, this paper demonstrates that this new series of peptoid inhibitors containing a free C-terminal carboxylate could be extended to other pharmacologically interesting enzymes.

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