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A tetradecapeptide somatostatin dicarba-analog: Synthesis, structural impact and biological activity

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ABSTRACT

We described here the first tetradecapeptide somatostatin-analogue where the disulfide bridge has been replaced by a carbon–carbon double bond. This analogue was prepared using microwave assisted ring closing metathesis (RCM) using the 2nd generation Grubbs as catalyst. Under our optimized conditions the cyclization between allylGly 3 and 14 proceeded in moderate yield, excellent cyclic/linear ratio and very high *Z*-double bond selectivity. NMR studies also demonstrated that the conformational flexibility of this peptide is increased in comparison to that of the natural hormone. Remarkably, this alkene-bridged somatostatin analog is highly selective against somatostatin receptors 1 and 5, suggesting that conformational rigidity is not required for the efficient interaction of somatostatin analogues with these two receptors.

Disulfide bonds are essential structural motifs found in proteins and many naturally occurring cyclic peptides. Hormones such as insulin,[1] oxytocin,[2] HGH[3] or somatostatin[4] are examples of molecules containing key disulfide bonds that highly contribute to their conformational stability. However, disulfide bonds can be easily reduced by disulfide isomerases or agents with sulfhydryl groups lowering the life span of disulfide containing molecules in vivo. To overcome this drawback, several disulfide bond mimetics such as Lanthionine derivatives,[5] carbon–carbon bonds,[6,7] triazole bridges[8] or direct head-to-tail amide bond cyclization[9] (cyclic peptides) have been developed. Successful examples of carbon–carbon surrogates of disulfide bonds include dicarba-analogs of insulin,[10] oxytocin[11] and HGH fragments,[12] all showing an enhanced metabolic stability without drastically modifying their biological activity.

The tetradecapeptidic hormone somatostatin[4] (also called somatotropin release-inhibiting factor SRIF) is involved in multiple biological functions, mediated by its direct interaction with at least five different G-protein coupled receptors, named SSTR1-5.[13] Its short half-life (2–3 min in plasma) and broad affinity for the five receptors have fostered the research of more stable and selective analogs (Fig. 1).

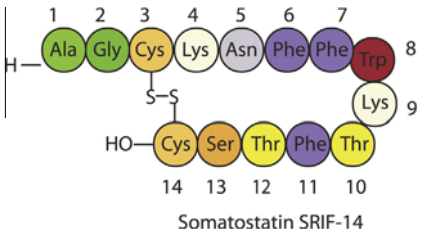

Figure 1. Amino acid sequence of somatostatin.

The discovery of the pharmacophore region[14] is the reason why most of the analogs developed so far are octa or hexapeptides. Among them, octreotide (Sandostatin®), lanreotide (Somatuline®), vapreotide (Sanvar®) and pasireotide (Signifor®) have reached the market.[15] Some dicarba-octreotide synthetic analogs have been developed in the last years.[16,17] Although they had an increased stability with respect to octreotide, the receptor affinities were reduced. In recent years we have designed new somatostatin analogs with improved selectivity and stability.[18,19] Our approach was based on the introduction of unnatural amino acids into the natural SRIF-14 scaffold and in the determination of their structures in solution by NMR spectroscopy. So far we have studied Qla [3-(3′-quinolyl)alanine] and Msa as surrogates of Trp and Phe,

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