Guanidine Motif in Biologically Active Peptides

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Abstract

In the last decade guanidines have attracted attention as valuable hydrogen bond-based catalysts while they have long been considered as organic superbases with a broad scope of synthetic applicability. Their easy modification has also expanded their capacity to form complexes with a wide range of metal salts as effective metal scavengers. All these attractive aspects have promoted a huge growth of this area in the field of organic synthesis and examples of such reactions have been collected in numerous reviews and some books. Moreover, this structural motif is also present in a large number of natural products and biologically active compounds, which exhibit appealing properties and play important roles in medicinal chemistry. In this highlight, we will only cover the synthesis and properties of biologically active guanidine containing peptides reported in the last three years.

1 Introduction

The guanidine motif is present in a great number of natural compounds that carry out different and important functions in animals and plants (Fig. 1).^[1] Due to their appealing properties, many research groups are working on the synthesis of these natural products and their derivatives, as well as exploring new properties and novel potential uses that they might exhibit.^[2] Among these interesting uses, guanidines have been mainly explored as efficient “superbases” for organic synthesis,^[3] useful organocatalysts,^[4] exchange membrane transporters,^[5] and peptides or peptide mimetics,^[6] which is the main topic of this highlight. Additionally, many guanidinium compounds have been employed as viable targets for drug discovery due to their potent biological activities.^[1]

Fig. 1 Active guanidine skeletons in natural compounds: 1,^[7] 2,^[8] 3,^[6d] 4,^[9] 5^[10] and 6.^[11]

This highlight will focus on a specific part of this huge and interesting field: peptides containing the guanidine motif, covering the most significant reported work since 2010.^[12]

2 Synthesis

There is a great number of peptides containing guanidine moieties within their structures. Due to this fact, there are several common synthetic strategies for introducing the guanidine group into peptides. The most common approach is adding an electrophilic amidine species to a peptide possessing an amine group that can act as a nucleophile.^[13] In spite of the possible drawbacks related to the synthesis of peptides, such as their high insolubility, the presence of different active functional groups, the need for protecting groups, as well as the position and steric hindrance of the nucleophilic amine, some selected peptides have been obtained following the methods disclosed below:

- a. Protected thiourea^[14] or *S*-alkyl-iso-thiourea^[15] derivatives are guanylating agents in this type of transformation (Fig. 2). Normally, these reactions are carried out with HgCl₂ as the catalyst and an organic base, providing good results with moderate to excellent yields. These guanylating agents are synthesized in high yield from easily available precursors, since

thioureas are very versatile starting materials. However, a strong electron-withdrawing group is required to activate the thiourea and the *N,N'*-bis-Boc-protection, which is easy to remove, seems to be the most general approach. Bis-protected thioureas are found to be effective with unreactive amines, such as aromatic amines. This approach is also useful for the synthesis of terminal guanidines; however, there are often more difficulties with the synthesis of internal amines. *S*-alkyl-iso-thioureas have been used successfully for the preparation of disubstituted guanidines under Mitsunobu conditions with moderate to excellent reactivities.

Fig. 2 Substituted biologically active guanidine peptides: **7**,^[16] **8**,^[17] **9**,^[18] and **10**.^[19]

- b. Other common reagents used for guanylation of peptide derivatives, without using HgCl_2 , are 1*H*-pyrazole-1-carboxamides (Fig. 3).^[20] This is an appealing and straightforward approach due to its operational simplicity and the mild reaction conditions employed in these syntheses when compared with other procedures. These processes only require stoichiometric amounts of the guanylation agent and an equimolar amount of an organic base, leading to attractive peptide structures in good to excellent yields. Moreover, these reagents exhibit enough reactivity for solid-phase peptide synthesis where other guanylation agents fail to do so. Although they have been found less active against sterically hindered secondary amines and more extreme

conditions are required to guanylate anilines, they can still be used efficiently in the presence of a variety of functional groups.

Fig. 3 Synthesis of guanidine containing peptides using 1*H*-pyrazole-1-carboxamidine: **11**,^[21] **12**,^[22] and **13a-13b**.^[23]

- c. Another interesting method is using *N,N'*-di-Boc-*N''*-triflylguanidine as the guanylation agent (Fig. 4).^[24] This is a simple method in which the guanylation agent is added to a solution containing a slight excess of a nucleophilic amine and one equivalent of a tertiary amine. Remarkably, these reactions proceed more quickly in nonpolar solvents (CH_2Cl_2 and $CHCl_3$), although other common procedures use polar solvents, and afford good yields with remarkably pure crudes. They could be performed either at room temperature or by heating the solution via conventional methods or in a microwave. Primary amines react more quickly than highly sterically hindered amines; however, anilines react more slowly but afford excellent yields after longer reaction times. In general, *N,N'*-di-Boc-*N''*-triflylguanidine exhibits better reactivity when compared with other guanylation agents, making it an interesting option for the synthesis of protected guanidines.^[24a]

Fig. 4 Synthesis of guanidine containing peptides using N,N' -di-Boc- N'' -triflylguanidine: **14**^[25] and **15**.^[26]

- d. There are other useful guanylation agents that can be used as an alternative for the above mentioned agents. In those reactions, a nucleophilic amine would be added to carbodiimide derivatives,^[27] *O*-methylisourea^[28] and benzotriazole derivatives,^[29] among other reagents. The latter is easily accessible from commercially available *S*-alkyl-iso-thiourea, and it is the most reactive guanylation agent due to the leaving group character of the benzotriazole moiety. It is highly efficient for guanylation primary and secondary amines, including anilines and solid supports.^[30] On the other hand, carbodiimide derivatives are synthesized from the corresponding urea or thiourea, which allows the preparation of chiral and different substituted carbodiimides, extending the scope and complexity of final guanidine derivatives.

Fig. 5 Synthesis of guanidine containing peptides using additional guanylation agents: **16**,^[31] **17**,^[32] and **18**.^[33]

- e. Guanidines have also been involved in Mitsunobu reactions as a crucial step for the synthesis of interesting compounds (Fig. 6).^[34] In these Mitsunobu reactions, contrary to the methods listed before, the guanidine group acts as a nucleophile, exchanging an alcohol group for a guanidine group.

Fig. 6 Synthesis of guanidine containing peptides using a Mitsunobu reaction.^[35]

It is remarkable that besides normal approaches carried out in solution, many examples of the abovementioned syntheses were performed using solid-phase processes.^[36] In general, these methods have been used extensively and have been proven useful for the synthesis of non-peptide analogues.^[2]

3 Molecular Recognition

Guanidine based sensors have attracted the attention of many research groups due to their usefulness in molecular recognition. This intriguing property has its roots in the guanidine moiety's ability to form multidentate bonds with its NH groups, resulting in a strong interaction that leads to the recognition of many functional groups. In this context, few examples of the use of peptidic compounds bearing guanidine groups as sensors for different types of compounds have been reported in the last few years.

Schmuck's group reported the use of a guanidinium-containing artificial peptide **20** as a nucleotide sensor (Fig. 7). Successful results for the recognition of phosphates and nucleotides derived of adenosine, guanosine, cytidine and uridine are reported. It is remarkable that the experiments are carried out in water at neutral pH, which might be useful for studies in physiological fluids. Additionally, this method can distinguish between adenosine monophosphate (AMP), diphosphate (ADP) and triphosphate (ATP), opening a wide range of possibilities for further biochemical research on biological mechanisms involving these species.^[37]

Fig. 7 Active guanidinium receptor.

Moreover, Zondlo and coworkers modified arginine residues and added them to peptide chains **18** (Fig. 5). This work showed the specificity and affinity of the synthesized peptides for different SRC Homology 3 (SH3) domains. This specificity depended on the position of the modified arginine group, its stereochemistry, and the length and substituents of its side-chain. Altering the side-chain of the arginine amino acids allowed for the important development of specific binding of different arginine derivatives to either the Src or the Grb SH3 domains.^[33]

4 Biological Properties

It is known that the properties of these peptides are dependent upon the guanidine functional groups of their structures.^[38] A small modification in the peptide skeleton could lead to the inactivation of the peptide or a change in its biological properties. One interesting feature is that this type of compound shows good cell penetrating properties, and that makes these peptides suitable for carrying external agents across cell-membranes (such as **11** and **13a,b** in Fig. 3).^[21,23,39]

Some of these molecules exhibit antibacterial properties, such as ureidomuraymycidine derivative **9** synthesized by Kurosu and coworkers (Fig. 2).^[18] This peptide might be a good precursor for synthesizing different muraymycins, which are natural compounds that inhibit the enzyme MraY, an essential enzyme for the biosynthesis of the polymer peptidoglycan (PG). This polymer is present in bacterial cell walls and it is vital for the survival of these microorganisms, hence the importance of further studies on this kind of peptide as antibacterial agents. Cyclic depsipeptide LI-F04a **19**^[35] also displays promising activity against different fungi and Gram-positive bacteria (Fig. 6).

Other peptides containing guanidines show opioid activity. In all cases, changes in the guanidine groups lead to different binding properties with the opioid receptors *in vivo*^[19] and *in vitro*^[40] studies. This is a really interesting property because these peptides might be a good alternative for the opiates that are currently being used in some treatments with extremely undesirable side effects, such as treatments for cocaine addiction.

Martin, Frankel and coworkers developed a series of arginine derivatives **7** that were shown to be protein arginine *N*-methyltransferases 1 (PRMT1) and PRMT6 inhibitors (Fig. 2).^[16] PRMTs are important due to their key role methylating arginine groups of DNA and RNA-binding proteins, like small nuclear or heterogeneous nuclear ribonucleoproteins (snRNPs or hnRNPs) and histones, which is an important process in the modulation of both RNA metabolism and transcription. Therefore, it is not surprising that PRMTs play an important part in the modulation and development of certain diseases, such as cancer and cardiovascular diseases, as well as in viral replication. Such properties make PRMTs attractive possible targets for many substances that interact with their active sites. This approach is really interesting because changes in the way that the guanidine groups of certain peptides interact with the active sites of PRMT1 and PRMT6 are observed. Changes in the guanidine group of the peptide, such as the incorporation of an ethyl group with a different number of fluorine atoms, lead to a promising inhibition of these PRMTs.

Moreover, Steinmetzer and coworkers synthesized diverse peptides **21** containing arginine residues that work as furin protease inhibitors (Fig. 8).^[41] These inhibitors are involved in important functions in the human body, such as the maturation of prohormones, proenzymes and other proproteins in the secretory pathway, carrying out a vital function in embryogenesis and homeostasis. Furthermore, furin is believed to be implicated in the development of many diseases including cancer, dementia and neurodegenerative

disorders. Small changes in the arginine amino acids or in their stereochemistry provide notable differences in their inhibition of furin.

Fig. 8 Biologically active guanidine containing peptides.

Furthermore, Burov and coworkers developed amino acid and peptide derivatives attached to creatine by peptidic bonds **22** (Fig. 8).^[42] Creatine and its analogues have shown neuroprotective activity in experimental models of brain stroke, but without a specific creatine transporter (CRT) they cannot cross the blood-brain barrier (BBB) efficiently. The compounds reported by these authors show promising neuroprotective activity in brain stroke models, both before and after ischemia, which makes them a good starting point for the further development of drugs used in stroke treatment. Also, Millo and coworkers developed an easy synthesis of different creatine derivatives **12** (Fig. 3), affording a wide range of appealing compounds in good yields and under mild reaction conditions.^[22] This work might be an attractive reference for the synthesis of many creatine analogues and their application in the treatment of neurological diseases.

In addition, Mammi and coworkers studied the biological effect of different peptides with chains of 11 amino acids (H-Aib-Val-Aib-Glu-Ile-Gln-Leu-Nle-His-Gln-Har-NH₂) containing a guanidine group in the N-terminal fragment.^[43] This research explored the increase of bioactivity and binding of parathyroid hormone (PTH) (1-11) analogues. These peptides, which contain 11 amino acids, are synthesized emulating the signaling domain of the PTH, corresponding to the N-terminal extracellular domain of the hormone composed by residues 1-11. This research is interesting because it complements previous studies which pointed to similar compounds as possible anabolic drugs,^[44] among other pharmacological properties.

5 Conclusion

We have briefly pointed out the most relevant examples reported in the last three years in the field of guanidine containing peptides. The above mentioned easy and versatile methodologies for guanylating a

wide range of compounds might be a good starting point for those who aim to synthesize and explore the properties of these interesting compounds. Moreover, it will not be a surprise when the number of works regarding this topic rises over the next few years due to all the appealing and only partially explored properties that different guanidine containing peptide groups show. Although they have already been proven useful in many remarkable biological studies, as disclosed above, researchers in the near future will be able to discover even more new and fascinating applications for these compounds.

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