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Solid-phase based synthesis of biologically promising triazolyl aminoacyl (peptidyl) penicillins

Patricia G. Cornier, Dora B. Boggián, Ernesto G. Mata *, Carina M.L. Delpiccolo

Instituto de Química Rosario (CONICET-–UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, 2000 Rosario, Argentina

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ABSTRACT

An efficient and versatile methodology for the preparation of valuable triazolyl aminoacyl (peptidyl) penicillins is described. Solid-phase Cu(I)-catalyzed Hüisgen 1,3-dipolar cycloaddition was used as the key step showing general applicability and excellent regioselectivity either with CuI or $[Cu(CH_3CN)_4]PF_6$ as Cu(I) source.

The main challenge in medicinal chemistry is to build libraries of compounds during the process of drug discovery, so the development of methodologies for a rapid and efficient construction of molecular diversity has been a priority during the last decade.[1] One of those methodologies is the parallel solid-phase synthesis that has been an important tool in order to improve the efficiency of drug discovery. After its initial use in the preparation of peptides, solid-phase organic synthesis is now extensively employed for the preparation of a range of biologically interesting molecules including heterocycles and natural product scaffolds.[2]

Hybrid constructs from the entities of known biological activity could be another important source for molecular diversity. This is a very promising approach in the development of leads for medicinal chemistry applications, which benefits from the intrinsic activity of all or part of the components of the hybrid.[3]

As part of our interest in the application of solid-phase techniques to biologically interesting molecules,[4] we envisaged that 1,3-dipolar cycloaddition could be useful for the conjugation of peptides to a penicillin derivative,[5] resulting in the triazole compounds bearing several points of diversity as shown in Figure 1.

The synthesis of 1,2,3-triazoles is clearly the most useful 'click reaction' discovered so far,[6,7] providing a very attractive possibility for (bio)conjugation reactions since, in general, it can be performed at mild conditions as well as biological media. Also, the 1,2,3-triazole moiety has several good properties: high chemical stability (hydrolytic, oxidant, and reducing conditions), aromatic character, good hydrogen-bond-accepting ability and this moiety is relatively resistant to metabolic degradation. This structure is found in a lot of biological active compounds: antimicrobial,[8] antiallergic,[9] anti-inflammatory, anticancer,[10] and anti-HIV agents,[11] as well as a new series of selective human β_3-adrenergic receptor agonists.[12] Additionally, 1,2,3-triazoles are found in herbicides, fungicides,[13] and dyes. Click reactions have been very successful in the synthesis of (bio)polymeric materials for biomedical and pharmaceutical applications.[14] Among other applications, peptides are used to facilitate transport across the cell membranes and to produce protein–protein interactions.[15] Besides, peptidotriazoles were reported as novel inhibitors of the growth of *Leishmania mexicana*.[16] On the other hand, β-lactam is arguably one of the most important heterocyclic skeletons in organic chemistry.[17] Since the discovery of penicillin, more than seven decades ago, a number of monocyclic and bicyclic β-lactams have found broad applicability in antibacterial therapy.[18,19] β-lactams can be referred as 'privileged structure' since many non-antibacterial activities have been found in their derivatives: inhibition of cholesterol absorption,[20] prostate specific antigen,[21] thrombin,[22] human cytomegalovirus protein,[23] cysteine protease,[24] and human fatty acid amide hydrolase,[25] as well as anticancer activity[26] and neuroprotective action.[27]

To achieve our objectives, several conditions of catalyzed 1,3-dipolar cycloaddition between terminal alkynes on solid support and penicillin azide were investigated.[28] Thermal cycloaddition conditions have a very high activation energy, therefore more energetic reaction conditions are required, leading to a mixture of both 1,4- and 1,5-regioisomers of 1,2,3-triazole. Softer conditions and better regioselectivity could be achieved using catalysis, such as the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC).[16,29] The major drawback of this reaction in the

* Corresponding author. Tel./fax: +54 341 4370477.
E-mail address: mata@iquir-conicet.gov.ar (E.G. Mata).

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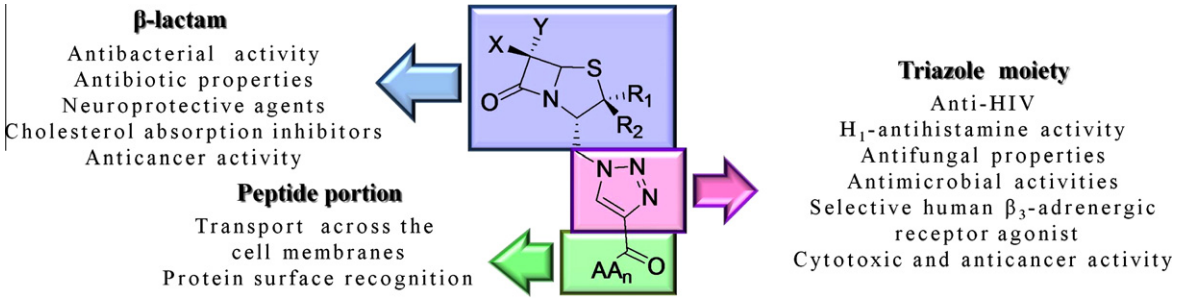
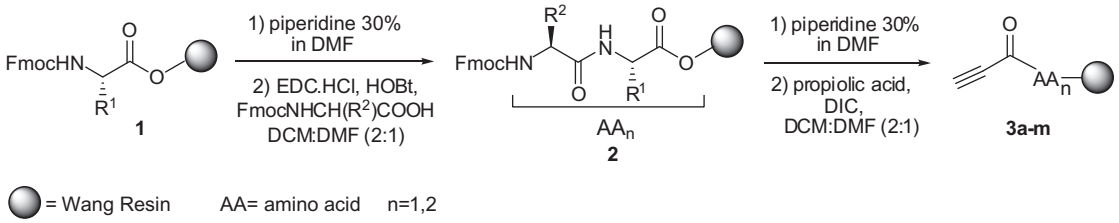


Fig. 1. Intrinsic biological properties of the building blocks.



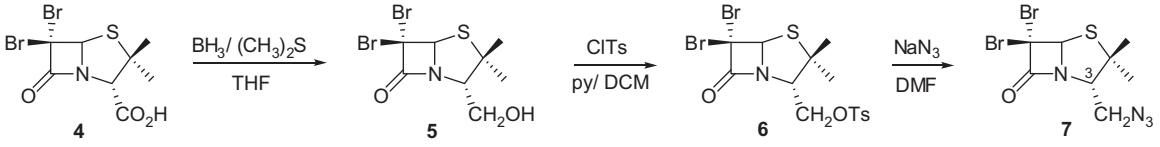
Scheme 1. Synthesis of alkyne-supported component.

homogeneous phase is the homocoupling products from two terminal alkynes.[30] Having the alkyne anchored to solid support, site isolation makes the homocoupling a considerably less favorable process.

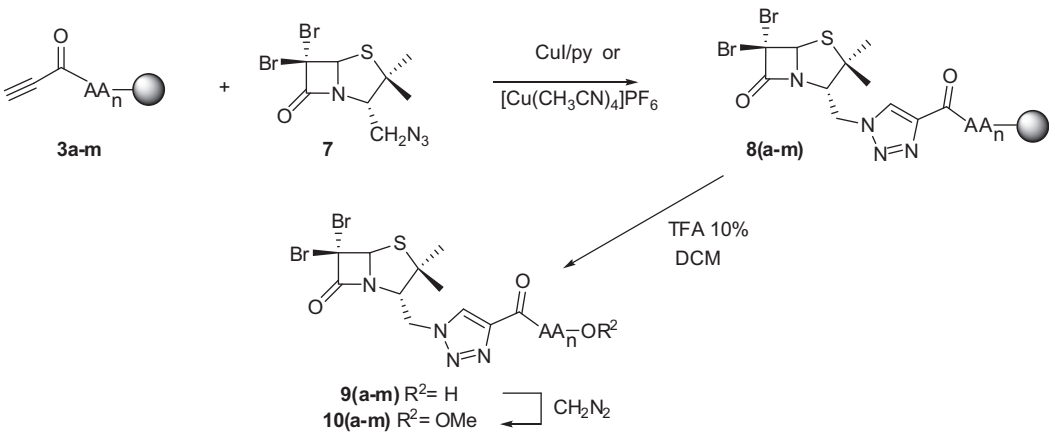
Our strategy started with the Fmoc protected-amino acid preloaded to Wang resin (**1**) which was treated with 30% piperidine in DMF to free the amino group (Scheme 1). In case that a second amino acid was coupled, standard solid-phase peptide synthesis conditions (EDC, HOBt) were used. Then, the resulting immobilized amino acid (peptide) was acylated with propiolic acid and *N*,*N*′-diisopropylcarbodiimide (DIC) as activating agent, leading to the terminal alkyne **3**.

On the other hand, the synthesis of azide component starts with the selected penicillanic acid **4** that was reduced with borane–dimethyl sulfide complex to afford the corresponding alcohol (**5**) (Scheme 2).[31] Tosylation of **5** followed by azide displacement gave the desired 3-(azidomethyl)penam derivative **7**.

Although the solid-phase Cu(I)-catalyzed Hüisgen 1,3-dipolar cyclization usually proceeds in high yields, it has been reported to be highly dependent on the substrate and reaction conditions.[32] Using the immobilized *N*-propiolyl glycine (**3a**, AA = Gly, $n = 1$, Scheme 3) as a model alkyne, the most suitable conditions to carry out the cyclization with azide **7** were explored. The immobilized penicillin–triazole conjugate obtained was cleavage from the solid



Scheme 2. Synthesis of azide component.



Scheme 3. 1,3-Dipolar cycloaddition between azides and immobilized alkynes.