Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 16 (2006) 6360–6362
Bioorganic & Medicinal Chemistry Letters

Desosamine in multicomponent reactions

Sepp Achatz[b] and Alexander Dömling[a,*]

[a]ABC Pharma, Franckensteinstr. 9a, 81243 München, Germany
[b]Morphochem AG, Gmunderstr. 39, 81379 München, Germany

Received 31 March 2006; revised 3 July 2006; accepted 5 July 2006

Abstract—Ubiquitously in natural products occurring desosamine is introduced into isocyanide based multicomponent reaction chemistry. Corresponding products are of potential interest for the design of novel antibiotics.

Many natural products are glycosylated and their biological activity is crucially dependant on the glycosylation. The amino sugar desosamine occurs in diverse natural products with different activities, for example, in the antibiotics tylosin **1** with mycaminose structurally related to desosamine, erythromycin **2** and methymycin **3**. SAR studies indicate that the disappearance of the sugar moiety leads to biologically inactive molecules. Recent structural elucidation of the binding mode of desosamine containing antibiotics (clarithromycin, erythromycin, azitromycin and tylosin) towards the ribosome can help to further understand the role of this amino sugar.[1] Based on these studies a net of hydrogen bonds and an ionic interaction is responsible for the strong binding of desosamine towards the ribosome, the primary target of this group of antibiotics (Fig. 1). Besides direct binding involvement towards the target one has to assume a considerable role of desosamine in the solubility and pharmacokinetic of the natural product.

The prokaryotic ribosome is sufficiently different form the eukaryotic one and thus comprises a major validated antibiotic target. More than 40 different antibiotics have been characterized to bind to the ribosome.[2] Several of those belong to the economically very successful antibiotics.

Based on the direct binding of desosamine onto the ribosome and the available structural data we envisioned to prepare small molecular weight compounds containing the desosamine unit.

In the past, we collected a lot of experience in the synthesis of libraries using MCR chemistry.[3] MCRs have intrinsic advantages making them highly useful in discovery and medicinal chemistry, such as superior accessible chemical space and time and effort to outcome ratio.[4]

Here, we show pilot preparative studies towards this goal, involving the gram scale preparation of 2-amino desosamine and first compounds based on Ugi's tetrazole scaffold.

Desosamine can be prepared on a gram scale by acid hydrolysis from readily available erythromycin (Fig. 2).[5]

Having established a convenient gram scale synthesis of desosamine we started to prepare building blocks based on the desosamine moiety useful as starting materials for multicomponent reactions, such as the primary amine and the isocyanide (Fig. 3).[6] First, the Kochetkov reaction of glycosides with ammonium carbonate in water at room temperature served to prepare 2-aminodesosamine.[7]

For the synthesis of compounds based on MCR backbones, we initially investigated the α-aminomethyl tetrazole scaffold based on an Ugi reaction (Fig. 4).[8] This backbone has the advantage to yield a secondary amine derived from the primary amine input and thus to maintain the solubility and basic character of the target compounds. Thus Ugi-tetrazole based compounds have been proven to show excellent ADME properties in the past.[9]

Keywords: Desosamine; Ribosome; Antibiotic; Multicomponent reaction; Isocyanide; Tetrazole.

* Corresponding author. E-mail: alexander.doemling@abc-pharma.de

0960-894X/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.bmcl.2006.07.017

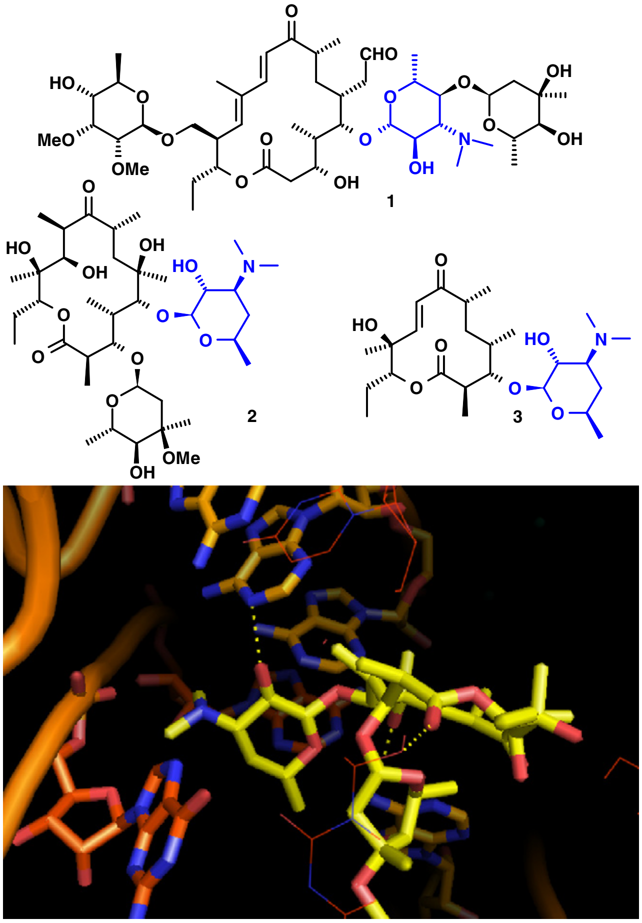

Figure 1. Above: Desosamine in different natural products. Below: Binding of the desosamine moiety of erythromycin to the ribosome (pdb ID: 1JZY). The 2′-OH contributes three hydrogen bonding to N6 and N1 of A and N6 of another A. The 3′NMe$_2$ forms a salt bridge with a phosphate of a G. Overall desosamine is involved in four hydrogen bonds and one salt bridge. The model was created using PyMol (www.pymol.com).

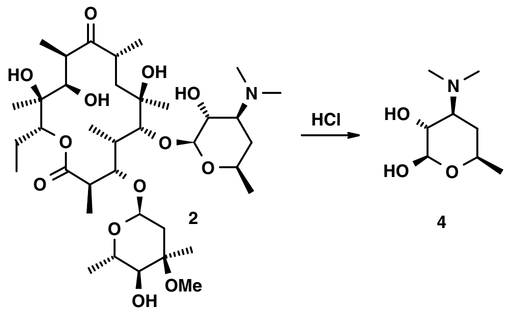

Figure 2. Acid hydrolysis of erythromycin yields desosamine.

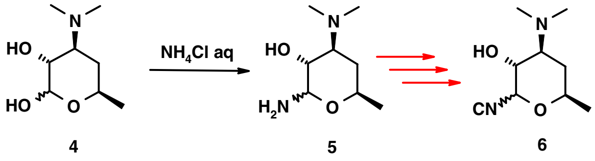

Figure 3. Preparation of 1-aminodesoasamine **5** from desosamine and ongoing synthesis of 1-isocyanodesosamine **6**.

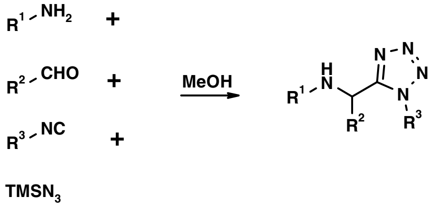

Figure 4. The synthesis of disubstituted α-aminomethyl tetrazoles according to Ugi.

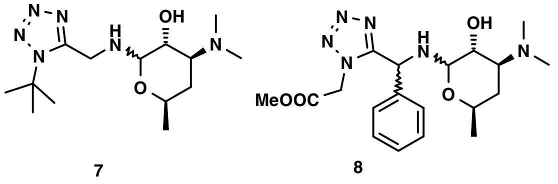

Figure 5. Two exemplary desosamine containing tetrazoles.

Synthesis of **7** and **8** was accomplished by the reaction of 1 mmol each of TMS-azide, aldehyde, 2-amino desosamine and the corresponding isocyanide in methanol at room temperature for 24 h. Evaporation of the solvent and concomitant chromatographic purification of silica gel yielded **7** and **8** as a mixture of diastereomers in 37% and 25% yield, respectively (Fig. 5).[10]

Disappointingly, screening of the two compounds **7** and **8** as mixtures of diastereomers against growth of the four representative gram positive and negative bacterial and fungal pathogens *Bacillus subtilis*, *Staphylococcus aureus*, *Candida albicans* and *Echerichia coli* at the three concentrations 50, 100 and 400 mM revealed no antibiotic activity.[11] The lack of activity might be explained by an inefficient cell penetration, efflux or no or bad recognition at the molecular ribosomal level for effective inhibition of protein biosynthesis.

In summary, we have synthesized 2-aminodesosamine from readily available erythromycin, by hydrolysis and subsequent aminolysis for the introduction in MCR chemistry. There are several points to mention. First, we introduced the amino sugar in the Ugi-4CR, the tetrazole variant, in initial experiments. Unfortunately the resulting compounds did not show any antibacterial activity in several bacterial and fungal strains. Second the combinatorial synthesis of arrays of desosamine containing organic molecules could lead to novel types of antibiotics interfering with the prokaryotic protein synthesis. Third, the described strategy could form an alternative to the introduction of desosamine containing polyketide libraries using glycosyltransferases.[12] Further studies are ongoing to produce novel antibacterials based on the outlined strategy and libraries derived from novel building blocks, for example, 1-isocyanodesosamine **6**.

References and notes

1. (a) Schlünzen, F.; Zarivach, R.; Harms, J.; Bashan, A.; Tocilj, A.; Albrecht, R.; Yonath, A.; Franceschi, F. *Nature* **2001**, *413*, 814; (b) Hansen, J.; Ippolito, J. A.; Ban, N.;

Nissen, P.; Moore, P. B.; Seitz, T. A. *Mol. Cell* **2002**, *10*, 117.

2. Wilson, D. N.; Harms, J. M.; Nierhaus, K. H.; Schlünzen, F.; Fucini, P. *Biol. Chem.* **2005**, *386*, 1239.
3. (a) Dömling, A. *Nucleosides Nucleotides* **1998**, *17*, 1667; (b) Beck, B.; Dömling, A.; Hess, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1701; (c) Beck, B.; Magnin-Lachaux, M.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2001**, *3*, 2875; (d) Henkel, B.; Sax, M.; Dömling, A. *Tetrahedron Lett.* **2003**, *44*, 7015; (e) Henkel, B.; Sax, M.; Dömling, A. *Tetrahedron Lett.* **2003**, *44*, 3679; (f) Henkel, B.; Westner, B.; Beck, B.; Mejat, B.; Dömling, A. *Tetrahedron Lett.* **2003**, *44*, 8947; (g) Beck, B.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2004**, *6*, 39; (h) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 4021; (i) Kolb, J.; Beck, B.; Almstetter, M.; Heck, S.; Herdtweck, E.; Dömling, A. *Mol. Div.* **2003**, *6*, 297; (j) Yehia, N.; Antuch, W.; Hess, S.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3121; (k) Antuch, W.; Menon, S.; Chen, Q.-Z.; Lu, Y.; Sakamuri, S.; Beck, B.; Schauer-Vukašinović, V.; Agarwal, S.; Hess, S.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2006**, *6*, 1740; (l) Dömling, A.; Herdtweck, E.; Heck, S. *Tetrahedron Lett.* **2005**, *47*, 1745.
4. (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321; (c) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (d) Hulme, C.; Nixey, T. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 921; (e) Dömling, A. *Chem. Rev.* **2006**, *126*, 17.
5. Wiley, P. F. *Methods Carbohydr. Chem.* **1962**, *1*, 257.
6. Dömling, A., unpublished.
7. Likhosherstov, L. M.; Novikova, O. S.; Derevitskaja, V. A.; Kochetkov, N. K. *Carbohydr. Res.* **1986**, *146*, C1–C5.
8. Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734.
9. Hulme, C. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley, 2004; p 332.
10. General procedure: 1 mmol of each isocyanide, desosamine, aldehyde, and trimethylsilylazide are stirred in 1 ml of methanol at 20 °C for 24 h. The solvent is evaporated and the residue is purified by silica gel chromatography (ethylacetate/hexane 1:1) to yield the corresponding products. The products where characterized by HPLC-MS and NMR. Compound **7**: $C_{20}H_{32}N_6O_2$: MS: $MH^+ = 389.2$; $M{+}Na = 411.2$. Compound **8**: $C_{14}H_{28}N_6O_2$: MS: $M{+}H^+ = 313.4$; $M{+}Na^+ = 436.4$.
11. Antibacterial screening method: The screening method used was designed to be high throughput. The test strains (*P. aeruginosa* ATCC 9027, *S. aureus* ATCC 6538, *C. albicans* ATCC 10231) where grown over night (at 35 °C in CASO bouillon: bacteria; at 20 °C in Sabouraud bouillon: *C. albicans*). The suspension is centrifuged (5000 µl min, 40 °C) and the pellet is resuspended in fresh medium and for another 2 h incubated. The suspension is then transferred into a 96 well plate and incubated with compounds. The cps where tested at 400 µM. The DMSO content is 5%. In the first column of a 96 well plate a 5% DMSO solution without cps refers to 100% growth. The growth in the presence of cps is determined by measuring the optical density at 550 nm in a plate reader at three different times: 0, 24, 48 h. The screening service was performed at Bioservice/Planegg/Germany.
12. Tang, L.; McDaniel, R. *Chem. Biol.* **2001**, *8*, 547.