Synthesis of multivalent aminoglycoside mimics *via* the Ugi multicomponent reaction†

Bernhard Westermann* and Simon Dörner

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The synthesis of multivalent neoglycoconjugates with 2,6-diamino-2,6-dideoxyglucose is accomplished by a flexible Ugi multicomponent approach leading to mono-, di- and tri-valent carbohydrate clusters.

Aminoglycosides such as neomycin B (**1**) or kanamycin B (**2**) are valuable antibiotics, that target prokaryotic RNA. It is believed that the β-hydroxyamine motif of these natural products interacts with the phosphodiester group (a) and the Hoogsteen site of RNA-residues (b), respectively (Fig. 1).[1] Unfortunately, resistance mechanisms and the toxicity have limited the applicability of this class of antibiotics severely. In order to overcome these drawbacks the groups of Wong and Tor fashioned new aminoglycoside surrogates by dimerisation of suitable aminoglycoside elements.[2] They enhanced the binding affinity between aminoglycosides and RNA by targeting multiple binding sites. Therefore, dimerized aminoglycosides can be considered as multivalent carbohydrate mimics. Through cooperative effects binding of these ligands can be improved quite drastically in comparison to their monovalent congeners.

In our approach presented in this communication we achieve aminoglycoside multivalency by using the Ugi multicomponent reaction (Ugi-MCR).[3] In addition we want to show that this approach leads to products exhibiting a great structural diversity. Based on previous findings by Wong *et al.* we incorporate 2,6-diamino-2,6-dideoxyglucopyranose moieties (ring I of neomycin B) which offer the appropriate binding motif as well as the possibility to achieve polycationic species under physiological conditions.[4]

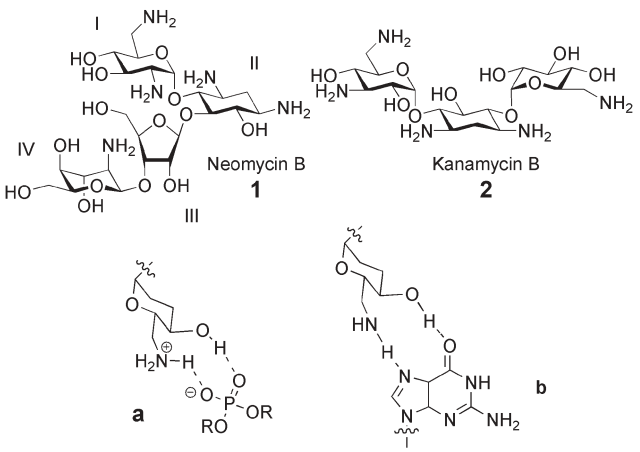


Fig. 1 Binding modes of aminoglycosides to RNA.

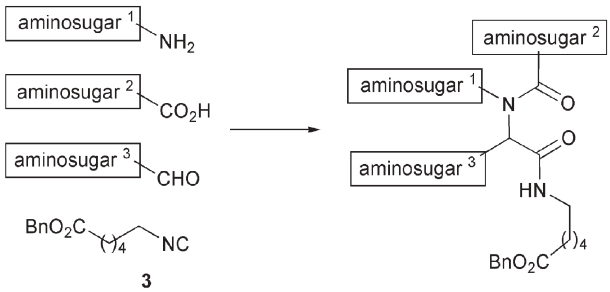
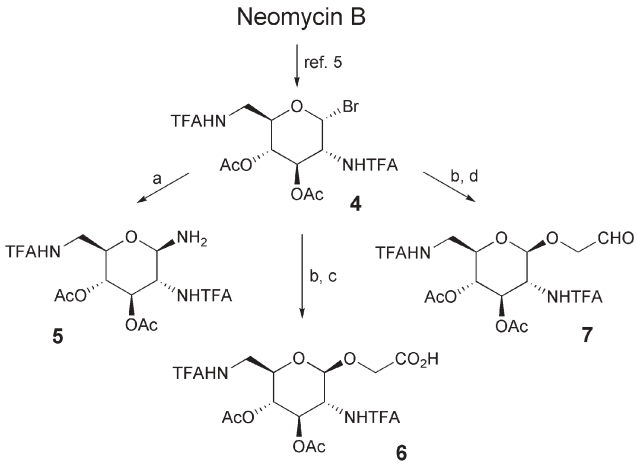


Fig. 2 The Ugi multicomponent reaction (U-4CR).

The Ugi reaction involves the combination of an amine, aldehyde, carboxylic acid and isocyanide in an one-pot process (Fig. 2).

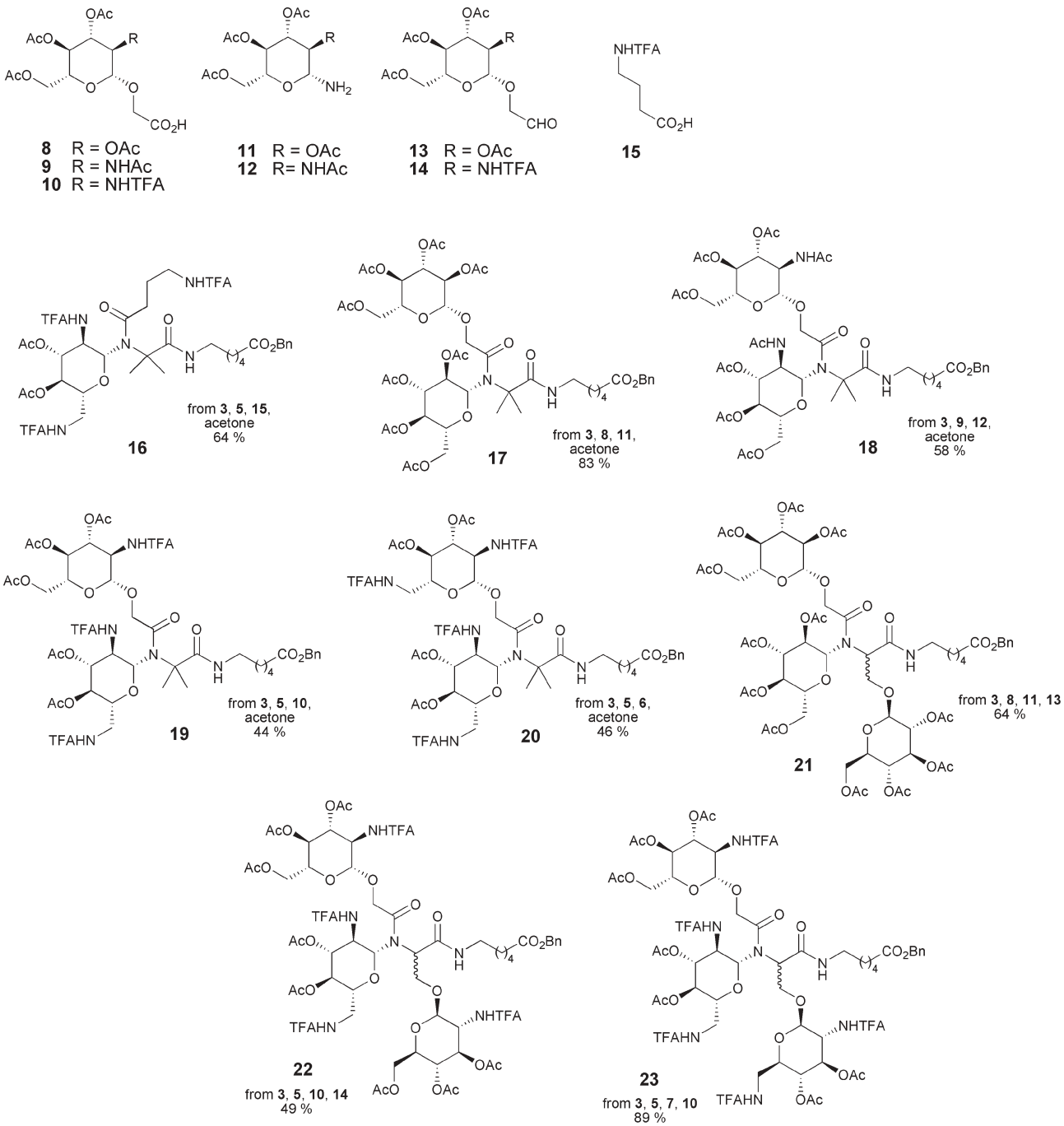
For the access to suitable 2,6-diamino-2,6-dideoxyglucose containing starting materials (amine **5**, carboxylic acid **6**, aldehyde **7**) we used the bromide **4** whose straightforward synthesis by degradation of moderately priced neomycin B is described by Hunziker *et al.*[5] We found that subsequent substitution of bromine by sodium azide under phase transfer conditions[6] followed by reduction furnishes amine **5** in very good yield. Based on the result of Kunz and Ugi[7] who employed



Scheme 1 Synthesis of Ugi-MCR building blocks with a 2,6-diamino-2,6-dideoxyglucose core unit. (a) i. NaN_3, Bu_4NHSO_4, DCM–$NaHCO_3$–H_2O, 86%, ii. H_2–PtO_2, MeOH, 94%; (b) i. AllOH, AgOTf, MS 4 Å, DCM, 40%; (c) $NaIO_4$, $RuCl_3 \cdot xH_2O$, CCl_4–CH_3CN–H_2O, 70%; (d) O_3, DCM, −78°C, then Me_2S, 99%.

† Electronic Supplementary Information (ESI) available: spectroscopic data and copies of NMR spectra. See http://www.rsc.org/suppdata/cc/b5/b501028d/

*bwesterm@ipb-halle.de



Scheme 2 Synthesis of multivalent aminoglycoside mimics.

glycosylamines in Ugi reactions we expected that **5** should be equally useful for that purpose. Starting from **4** Königs–Knorr reaction allows for the introduction of an *O*-allyl side chain which can be transformed into carboxylic acid **6** or aldehyde **7** by ruthenium catalyzed periodate cleavage or ozonolysis, respectively (Scheme 1). In all multicomponent reactions described in this communication isocyanide **3** has been used. It was synthesized starting from 6-aminohexanoic acid and offers superior reactivity compared to other isocyanides such as acetyl isocyanide. Furthermore, it can be utilized for later derivatisation.

In preliminary experiments, the Ugi-MCR of amine **5**, acetone, isocyanide **3** and *N*-trifluoroacetyl-protected γ-aminobutyric acid **15** provided monovalent product **16** in 64% yield.

To establish and optimize the reaction conditions, the corresponding glucose-derivatives **8**, **11** and **13** have been used (Scheme 2). It was found that carrying out the reaction in a 0.2 molar methanolic solution at room temperature was best with precondensation of the amine and the carbonyl compound leading to the di- and trivalent products **17** and **21** in 83 and 64% yield, respectively. After optimization the glucose based building blocks were successfully exchanged by protected amino sugars.

Employing under the same conditions amine **12** and carboxylic acid **9** which both contain a 2-deoxy-2-acetaminoglucose (GlcNAc) core unit, the yield of the divalent compound **18** was 58%. Molecules **19** and **20** exhibiting *N*-trifluoroacetyl-protected sugar units could be isolated in 44–46% yield. In analogy to test compound **21** trivalent aminoglycoside mimics **22** and **23** can be synthesized by replacing acetone with appropriate aldehyde building blocks and are isolated as diastereomeric mixtures in 49% and 89% yield. In all experiments the Ugi-product was the major reaction product formed. Noteworthy amounts of the corresponding Passerini-products were not detected.

In summary, we have developed a very straightforward and short synthesis to structurally diverse aminoglycoside mimics. By using the Ugi-MCR approach, different aminosugar units can be coupled in a very defined way. The ability of the unprotected products to bind to RNA targets has been evaluated by surface plasmon resonance spectroscopy and will be reported in due course.‡

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Bernhard Westermann* and Simon Dörner
Leibniz Institute of Plant Biochemistry, Department of Bioorganic Chemistry, Weinberg 3, 06120, Halle (Saale), Germany.
E-mail: bwesterm@ipb-halle.de; Fax: +49 345 5582 1309;
Tel: +49 345 5582 1340

Notes and references

‡ Typical experimental procedure: to a solution of amine **5** (0.6 mmol) in methanol (3 ml) is added acetone (0.6 mmol). The mixture is stirred for 1 h followed by addition of carboxylic acid **6** (0.6 mmol) and isocyanide **3** (0.6 mmol). After stirring for 48 h the solvent is evaporated and the crude product is purified on silica (eluent: ethyl acetate–hexanes) to give product **20** in 46% yield.

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