AROMATIC AMIDE DERIVATIVES OF VANCOMYCIN

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INTRODUCTION

In 1960, Abraham and Newton defined antibiotics as "compounds of natural origin produced primarily by microorganisms, characterized by high activity against pathogens, and relatively low toxicity to humans and animals, and resistance to inactivating enzymes and body fluids" [1].

Today, this term should be used for bio-based chemicals and their synthetic analogs, which work selectively to microorganisms [2]. The emergence of resistance to many antibiotics, such as β-lactams, macrolides, quinolones and vancomycin (Figure 1) is becoming a major health problem worldwide. When looking for new solutions in the treatment of vancomycin-resistant strains, we should pay attention to vancomycin dimers, which are usually a more reactive form showing a greater affinity for the dipeptide which connects to this antibiotic [3].

In connection with these reports, the purpose of our study was to carry out the reaction of two selected aromatic amines: *o*-phenylenediamine (Figure 2) and biphenyl-4,4'-diamine (Figure 3) with vancomycin for obtaining monomers and dimers.

The aim of this project is exhibiting antibacterial activity and improvement of properties against resistant bacterial strains.

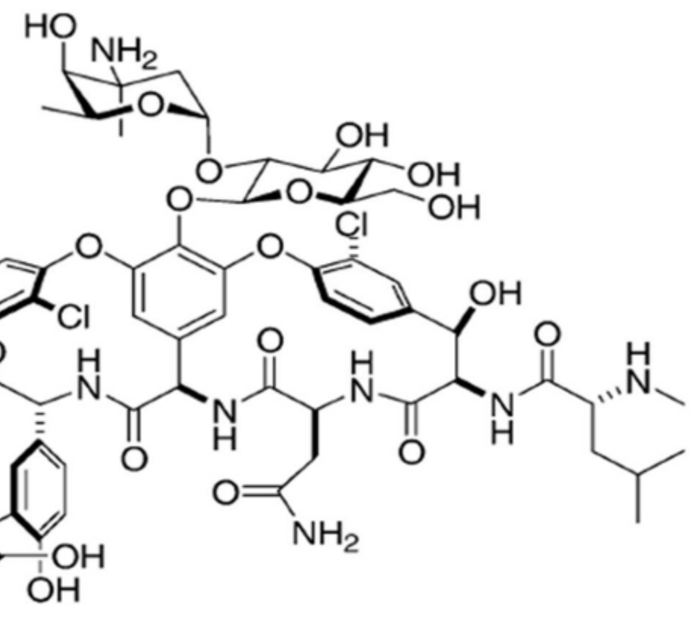


Fig. 1 Molecular structure of vancomycin.

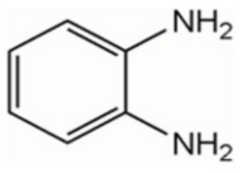


Fig. 2 Structure of *o*-phenylenediamine.

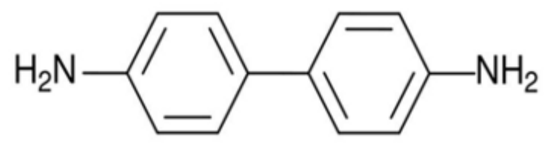
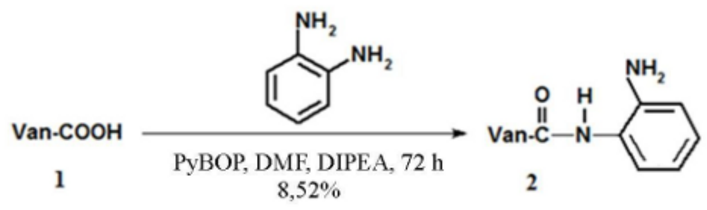


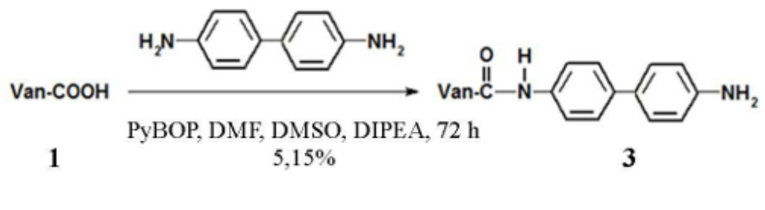
Fig. 3 Structure of biphenyl-4,4'-diamine.

Modification of free carboxyl group of cyclic heptapeptide with *o*-phenylenediamine and biphenyl-4,4'-diamine

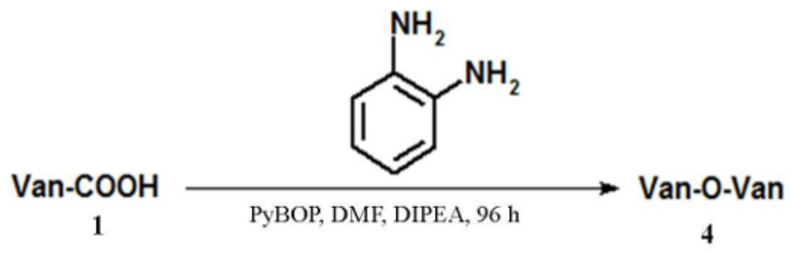
RESULTS AND DISCUSSION



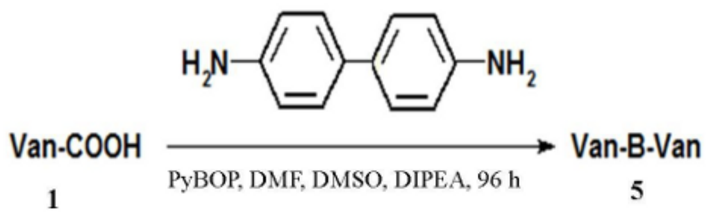
Scheme 1 Vancomycin monomer by *o*-phenylenediamine formation (**2**).



Scheme 2 Vancomycin monomer by biphenyl-4,4'-diamine formation (**3**).



Scheme 3 Vancomycin dimer by *o*-phenylenediamine formation (**4**).



Scheme 4 Vancomycin dimer by biphenyl-4,4'-diamine formation (**5**).

Synthesis of vancomycin monomer (Scheme 1) was started from using the vancomycin hydrochloride (Van-COOH) as a substrate and treating it with *o*-phenylenediamine, PyBOP, DMF and DIPEA what gave a derivative **2**. Synthesis of derivative **3** (Scheme 2) was started also from using the vancomycin hydrochloride (Van-COOH) as a substrate and treating it with biphenyl-4,4'-diamine, PyBOP, DMF, DMSO and DIPEA what gave a compound **3**. The structures of these vancomycin monomers were proven by MS. Usually on the spectra could find mass increased by Na or K $[M+Na]^+$ and $[M+K]^+$. For derivative **2** (Figure 6) it was $[M+H]^+$, $[M+Na]^+$ and $[M+K]^+$ 1540, 1562, and 1578, respectively when the MW it was 1539. For derivative **3** (Figure 7) it was also $[M+H]^+$, $[M+Na]^+$ and $[M+K]^+$ 1617, 1639 and 1655, when the MW it was 1616. For the purification of this obtained vancomycin monomers (Figure 4 and 5) we used HPLC (preparative HPLC: DIONEX Ultimate 3000, C8, 25 cm x 10 mm, flow rate 1.5 $mLmin^{-1}$, 10—80% CH_3CN, 20% 0,1% TFA in H_2O over 35 min).

Vancomycin dimers with *o*-phenylenediamine (Scheme 3) and biphenyl-4,4'-diamine (Scheme 4) were synthesized at the same method as described above for vancomycin monomers. Synthesis was started from vancomycin hydrochloride (Van-COOH) as a substrate and other steps were identical. We obtained two derivatives: vancomycin dimer with *o*-phenylenediamine (Van-O-Van) - compound **4** and vancomycin dimer with biphenyl-4,4'-diamine (Van-B-Van) - compound **5**. Amounts of these dimers were too small, so we didn't purify these compounds.

Modified this way monomers and dimers of vancomycin will be tested on VRSA strains.

We think that the new derivatives will have a better antimicrobial properties than those currently used, which will reduce the problem of resistance against Gram-positive glycoproteins.

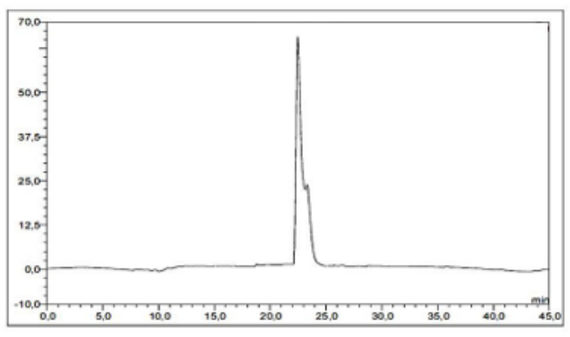


Fig. 4 HPLC chromatogram of the purified vancomycin monomer (**2**).

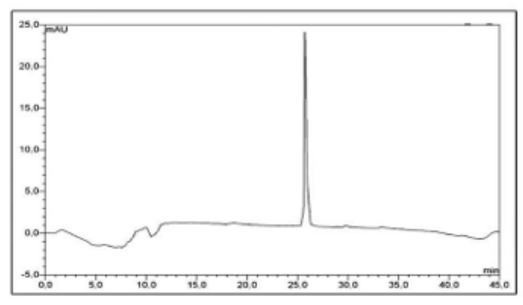


Fig. 5 HPLC chromatogram of the purified vancomycin monomer (**3**).

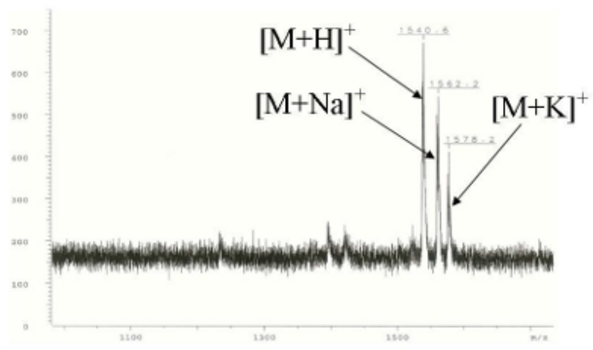


Fig. 6 The spectrum of MALDI-TOF MS of the purified vancomycin monomer (**2**).

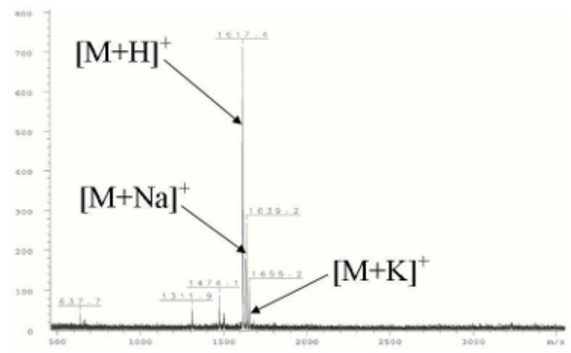


Fig. 7 The spectrum of MALDI-TOF MS of the purified vancomycin monomer (**3**).

CONCLUSIONS

1. The reactions we conducted were more effective in case of using coupling reagents such as PyBOP and DIPEA.
2. The best results were obtained for synthesis with higher amount of PyBOP and longer reaction time.
3. A good method of purifying vancomycin monomers is HPLC.
4. Methods of synthesis of vancomycin monomers and dimers require further modification.
5. Synthesis of vancomycin dimers may be more effective in case of using double amount of PyBOP.

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References:

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INNOVATIVE ECONOMY
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