SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Synthetic modifications of glycopeptide antibiotics

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The Examination takes place at the Library of Department of Pharmacology Faculty of Pharmacy, University of Debrecen
22nd July 2020 at 11 am

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
22nd July 2020 at 1 pm

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List of abbreviations

Boc: *tert*-butoxycarbonyl

CuAAC: copper(I)-catalyzed azide-alkyne cycloaddition

COSY: correlation spectroscopy

DMAP: 4-dimethylaminopyridine

EC_{50}: effective concentration

EDCI: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

ESI: electrospray ionization

HIV: human immunodeficiency virus,

HPLC: high performance liquid chromatography

HMBC: heteronuclear multiple-bond correlation spectroscopy

HSQC: heteronuclear single-quantum correlation spectroscopy

MALDI: matrix-assisted laser desorption ionization

MDCK: Madin-Darby Canine Kidney cells

MIC: minimum inhibitory concentration

MS: mass spectrometry/mass spectrum

NHS: *N*-hydroxysuccinimide

NMR: nuclear magnetic resonance

NOESY: nuclear overhauser effect spectroscopy

PyBOP: benzotriazole-1-yl-oxy-*tris*-pyrrolidino-phosphonium hexafluorophosphate

RP: reversed-phase

TEG: tetraethyleneglycol

TFA: trifluoroacetic acid

TOCSY: total correlation spectroscopy

TOF: time of flight

VAHP: vancomycin aglycone hexapeptide

VRE: vancomycin resistant *Enterococcus*

1. Review and aims of the dissertation

1.1. Literary review

Glycopeptides used in the antibacterial therapy are highly polar compounds with relatively large molecular weight, therefore they are primarily administered intravenously. Their most common indications include serious skin and soft tissue infections, wound infection prophylaxis, endocarditis, *Clostridium difficile* infection (*per os*). Glycopeptides on the market are only effective against Gram-positive bacteria.

In the second half of the 1980s, the isolation of vancomycin resistant pathogenic bacterial strains - mostly *Enterococcus* species - became more and more frequent. This became the starting point for the synthetic chemical transformations of vancomycin, with the aim of obtaining derivatives that are active against resistant pathogens. In the case of the vancomycin type of glycopeptides (vancomycin, chloroeremomycin) the predominant modification was the attachment of a lipophilic structural unit to the parent compound (e.g. by *N*-alkylation or *N*-acylation). In the case of compounds already containing the lipophilic part in their natural structure (teicoplanin, A-40926), the most relevant breakthrough was the modification of the *C*-terminus, primarily the introduction of basic groups through an amide bond. These traditional structural modifications resulted in the successful launch of the second generation of glycopeptides (telavancin, dalbavancin, oritavancin) that are now in clinical usage. To understand the mechanism of action of glycopeptides better, many other structural modifications were conducted on the parent compounds, e.g. removal of the carbohydrates, alkylation of the phenolic OH-groups, deamination, the transformation of the C-terminus into esters or hydrazides etc.

Besides the further synthetic modifications (e.g. the change of amino acids or the synthesis of covalent dimers) of the parent antibiotics beginning from the second half of the 1990s, the conjugation of glycopeptides with other antibiotics (e.g. beta-lactams) or molecules (e.g. transglycosylase inhibitors) also became more frequent. The aim of this latter was to obtain compounds with multiple sites and mechanisms of action.

The group V. of glycopeptides (kistamicins) are excellent anti-HIV and anti-influenza virus compounds. Based on this information, Russian researchers prepared semisynthetic glycopeptides from other structural groups, such as vancomycin, eremomycin and teicoplanin that proved to be active against HIV, hepatitis C and other viruses.

Researchers of the Department of Pharmaceutical Chemistry have been working on the semisynthetic transformations of glycopeptide antibiotics for a long time, with the aim of discovering derivatives that are active against glycopeptide resistant bacteria. The lipophilic, *N*-terminal triazole derivatives of the teicoplanin A_3-2 pseudoaglycone containing *n*-decyl and

biphenyl substituents had outstanding activity against glycopeptide resistant bacterial strains. The synthesis of antiviral derivatives is also a fundamental research area in our department. One of the squaric acid amide derivatives of ristocetin aglycone had exceptional activity against influenza virus strains besides a favorable selectivity index. Later, a similarly active, however more toxic derivative was also prepared from the teicoplanin A_3-2 pseudoaglycone.

1.2 Aims of current PhD research

One of the main aims of my doctoral research was the chemical modification of teicoplanin for obtaining new compounds with higher antibacterial activity than that of known derivatives. A great emphasis was put on achieving activity against glycopeptide resistant Gram-positive bacteria (VRE). This was primarily envisioned by the transformations of the functional groups of the aglycone, such as the *N*-terminal amino group or the *C*-terminal carboxyl group. Besides modifications known from the literature, reactions that have not been implemented to generate teicoplanin derivatives yet, were also planned to be used in order to accomplish the task.

In relation to this, the elaboration of a new, simple, low-cost and good yielding procedure for the preparation of TC (teicoplanin A_3-2) pseudoaglycone was planned, since this is the most frequently used parent compound for the synthesis of glycopeptide derivatives in our department.

As a continuation of a former research in our department, the preparation of additional *N*-terminal triazole derivatives of TC was planned. After that, further enhancement of the antibacterial activity was planned by transforming the *C*-terminus of the obtained derivatives.

The presence of a basic, positively charged *N*-terminus of glycopeptide antibiotics is considered to be an important factor in ligand binding. Based on this, the preparation of teicoplanin derivatives in which the basicity of the *N*-terminus is provided by guanidino groups instead of the amino group.

On the basis of literature data, the preparation of an aminoethylated glycopeptide derivative resembling the structure of polymyxins was planned in order to achieve activity against Gram-negative bacteria. The transformation was planned to be conducted on vancomycin aglycon hexapeptide (VAHP).

The synthesis and antibacterial evaluation of covalent teicoplanin dimers similar to the covalent vancomycin dimers found in the literature was also planned.

An important aspect when designing teicoplanin derivatives for antibacterial use was that the final products (or at least some of them) should have comparable key physicochemical properties to those of literature compounds (e.g. Mideplanin) which were proved to have favorable *in vivo* efficacy. For this the software MarvinSketch by ChemAxon was used. The built-in plugins

are very useful for the prediction of the logD value, pH-dependent net charge, thus the isoelectric point (pI) of peptides and the comparison of these parameters.

In order to prepare glycopeptide derivatives that are effective against influenza viruses and to gain structure-activity relationships, the systematic transformation of the *N*-terminal amino group of TC was planned. In relation to this, the synthesis of selective antiviral derivatives which are inactive against bacteria was also planned by using VAHP as starting material.

2. Applied methods

The course of reactions was followed by thin-layer chromatography. The compounds were purified by normal- or reversed-phase column chromatography, by preparative thin-layer or by gel chromatography. The structure of the compounds was confirmed by 1D (^{1}H, ^{13}C) and 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HSQC, ^{1}H-^{1}H TOCSY, ^{1}H-^{13}C HSQC-TOCSY, ^{1}H-^{13}C HMBC) experiments and by MALDI-TOF and ESI-TOF mass spectrometry. The composition of the multicomponent compounds was determined by analytical reversed-phase high performance liquid chromatography-mass spectrometry (RP-HPLC-MS). Chromatograms and mass spectra were evaluated using DataAnalysis 3.4 and flexAnalysis (Bruker), NMR spectra were evaluated using MestReNova or TopSpin softwares.

3. New scientific results of the research

3.1. New method to prepare teicoplanin A_3-2

The teicoplanin A_3-2 pseudoaglycone (TC) is a crucial starting compound for our department, therefore its preparation with good yield is essential. Due to the unavailability of hydrogen fluoride gas that was formerly used, a new method was to be found for the preparation of the pseudoaglycone containing the *N*-acetylglucosamine. After several attempts the optimal method proved to be the treatment of teicoplanin with concentrated hydrochloric acid at room temperature. After simple workup and column chromatography I obtained the product with the same purity and yield (cca. 75%). Additionally, the new procedure is considerably less expensive and easier to carry out.

3.2. Preparation of additional *N*-terminal 1,2,3-triazole derivatives of teicoplanin A_3-2

Although the *n*-decyl and biphenyl substituted triazole derivatives of teicoplanin A_3-2 (TC) formerly synthesized in our department were highly active *in vitro*, we wanted to investigate if it is possible to further enhance the activity by modifying the length and structure of the lipophilic part. Azido teicoplanin A_3-2 was prepared from teicoplanin A_3-2 by diazotransfer, then as analogues of the original *n*-decyl derivative, the *n*-hexadecyl-, *n*-dodecyl- and *n*-octyl variants were synthesized by Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC). As variants of the former derivative containing the biphenyl group the phenyl- and α-naphthyl derivatives were prepared. For the synthesis of two compounds with lipohydrophilic substituents, a protected galactose and lactose derivative were used as alkyne reactants.

Among the aliphatic analogues the most effective was the *n*-octyl derivative, surpassing the activity of the original *n*-decyl analogue even in the case of the teicoplanin resistant VanA *E. faecalis*. The activity of the phenyl and α-naphthyl derivatives was particularly encouraging. The compound containing the galactose derivative showed excellent activity against staphylococci, while the analogues with the bulky substituents were inactive, probably due to steric hindrance preventing the interaction of the binding pocket with the target peptide.

3.3. Synthesis of derivatives of teicoplanin A_3-2 (TC) with anti-influenza virus activity

3.3.1. *N*-terminal 1,2,3-triazole derivatives

By investigating the triazole derivatives described in the previous section for anti-influenza activity and cytotoxicity, it became obvious that these properties are highly dependent on the hydrophilic/lipophilic character of the substituents. Although the analogues with the longer aliphatic substituents displayed high activity, all of them were highly toxic to MDCK cells.

Analogues containing aromatic substituents showed moderate activity and cytotoxicity, regardless of bulkiness, while compounds with the carbohydrate substituents were only slightly/non-toxic with variable activity. We established that the cytotoxic effect increases proportionally to the length of the lipophilic side chains, which might be the result of the disruption of the cytoplasmic membrane.

Earlier, during my gradual work I synthesized an analogue of the antivirally inactive, but toxic *n*-decyl derivative, which contains a tetraethyleneglycol linker between the lipophilic part and the aglycon. This compound showed exceptionally good activity against influenza viruses, while also being far less toxic to MDCK cells, than the original compound. Based on this result, the *n*-octyl- , *n*-hexyl- and *n*-butyl analogues with the TEG linker was synthesized. The antibiotic analogues with the shorter alkyl chains were indeed less toxic, however, their anti-influenza virus activity was lost, as well.

3.3.2. *N*-terminal sulfonamide derivatives

A simple modification that have not been studied yet was the transformation of the *N*-terminus of TC into sulfonamide groups using different sulfonyl chlorides in the presence of pyridine. The products could be isolated with moderate (aromatic) and satisfactory (aliphatic) yields.

Multiple derivatives had notably high anti-influenza virus activity, though some of them proved to be considerably cytotoxic. Again, we could observe the gradual increase of activity in parallel with growing side chain length which was accompanied by increasing cytotoxicity. The most promising compound in this group seemed to be the *n*-hexanesulfonyl derivative, since besides its moderate cytotoxicity, it inhibited the viral infection of cells in a relatively low concentration.

In most cases, the *in vitro* antibacterial activity of the lipophilic sulfonamide derivatives was higher than that of teicoplanin or the TC pseudoaglycone, however none of them were as effective as the most active triazole derivative with the α-naphthyl group (Chapter 3.2.). Although their activity against *Staphylococcus* strains was similar (MIC 0.5-2.0 μg/mL), against *E. faecalis* strains, only five out of eight derivatives were more or less active.

3.4. Synthesis of teicoplanin derivatives with 4-(1-naphthyloxymethyl)1,2,3-triazole ring

After investigating the *in vitro* activity of glycopeptide derivatives of our department on a collection of 44 glycopeptide resistant *Enterococcus* strains, the most effective compound proved to be the triazole derivative of teicoplanin A_3-2 substituted with the α-naphthyl group. Since 2/3 of the *vanA* positive strains was completely resistant even to this compound, the optimization of its structure was continued. To this end (based on literature data) the aglycon, teicoplanin A_3-1 and

teicoplanin analogue of the original compound, plus the *C*-terminal amide derivatives of the four variants by condensing *N*,*N*-dimethyl-1,3-propanediamine or *N*,*N*-diethyl-1,3-propanediamine with the carboxyl group were prepared. I obtained the triazole derivatives by different acid hydrolysis reactions of teicoplanin, followed by diazotransfer and CuAAC reaction. The triazoles were converted into the required amide derivatives by PyBOP mediated amide coupling using the appropriate amines.

In the preliminary test of the *in vitro* antibacterial activity of the compounds, the amide derivatives of the TC (T-A_3-2) pseudoaglycone proved to be much more effective than the original compound, the aglycone or the TB (A_3-1) analogues. The least effective compounds were those obtained from the teicoplanin mixture. A few of the analogues were compared to vancomycin, teicoplanin and oritavancin in a test against 20 strains of glycopeptide resistant enterococci. The most active compound, essentially displaying the same *in vitro* activity as oritavancin was the diethylaminopropyl amide of the original TC derivative. Surprisingly, the teicoplanin mixture analogues were more active than we have anticipated based on the standard panel results.

3.5. Preparation of *N*-terminal guanidine derivatives of teicoplanin A_3-2 (TC) and teicoplanin

In order to preserve the basic character of the *N*-terminal amino group, the *N*-terminus was transformed into a guanidino group substituted by lipophilic moieties. For the synthesis of the new compounds different alkylamines were reacted with phenyl isothiocyanate, then the obtained thiocarbamides were treated with methanesulfonyl chloride in the presence of trimethylamine and a catalytic amount of DMAP, yielding the corresponding lipophilic carbodiimides. Using these reagents, four TC derivatives with the *C*-terminus converted into diethylaminopropyl amide were synthesized. Three additional dimethylaminopropyl amide derivatives from teicoplanin complex were prepared. In these the guanidino group was substituted by *n*-octyl-, 4-phenylbenzyl- or *N*-benzyl-piperidyl functions besides the unvaried phenyl group.

Compared to analogues with a free *C*-terminal carboxyl group prepared by others in our group the TC amides had a markedly lower activity against enterococci. Of the amides prepared from teicoplanin complex, the *n*-octyl variant inhibited the growth of every tested strain effectively, while the 4-phenylbenzyl analogue with comparable lipophilicity and the *N*-benzyl-piperidyl derivative proved to be active only against staphylococci.

3.6. Synthesis of anti-influenza virus derivatives of vancomycin aglycon hexapeptide

To synthesize selective antiviral compounds, six new derivatives were prepared by coupling the side chains of the three least toxic teicoplanin A_3-2 derivatives with the highest activity to vancomycin aglycon hexapeptide. Three of these are modified on the *N*-terminus, while the other three are the *C*-terminal variants. The aim of synthesizing these latter three was to determine whether the different position of the side chains on the aglycone influences the activity.

For the synthesis of the two *N*-terminal triazole derivatives, vancomycin aglycon hexapeptide (VAHP) was prepared from vancomycin by Edman degradation and deglycosylation. The hexapeptide was converted into the azido derivative by diazotransfer. The two selected side chains were coupled to the azido aglycon by CuAAC reaction yielding the two triazoles modified on the *N*-terminus. The *n*-hexanesulfonamide derivative was prepared by the simple reaction of VAHP and *n*-hexanesulfonyl chloride. For the synthesis of the two *C*-terminal triazole analogues, the alkyne form of the side chains was coupled with 2-azidoethylamine using click chemistry, while the suitable side chain for the synthesis of the sulfonamide analogue was prepared by the reaction of ethylenediamine and *n*-hexanesulfonyl chloride. The three side chains with a primary amino group were condensed with the carboxyl group of VAHP using PyBOP as peptide coupling reagent.

As expected, the antibacterial activity of each new compound was reduced to a negligible level, most probably due to the destruction of the D-Ala binding pocket. Of the six compounds only the two triazole derivatives displayed considerably good EC_{50} values (~2 μM) with cytotoxic concentrations to MDCK cells of about 20 μM (selectivity index cca. 10). The *N*-terminal *n*-hexanesulfonyl derivative and the analogues modified on the *C*-terminus were either inactive or only slightly active. The results proved that the site of attachment of the side chains to the aglycon has a huge impact on the anti-influenza virus activity of the compounds.

3.7. Synthesis of an aminoethylated, amphiphilic derivative of vancomycin aglycone

To break the intrinsic resistance of Gram-negative bacteria against glycopeptides, a basic vancomycin aglycon derivative carrying an *n*-decanoyl side chain and five aminoethyl groups, resembling the structure of polymyxins was synthesized.

By treating *n*-decanoic acid with thionyl chloride, the resulting acyl chloride was used for the acylation of D-leucine, yielding *N*-decanoyl-D-leucine. This compound was converted to an NHS active ester by EDCI·HCl mediated activation and *N*-hydroxysuccinimide. The active ester was used to *N*-acylate VAHP, resulting in *N*-decanoyl-norvancomycin aglycone. By coupling mono-*N*-Boc-ethylenediamine to the *C*-terminus of this peptide, an amide intermediate was obtained, the phenolic OH-groups were alkylated using *N*-Boc-bromoethylamine. The removal of

the protecting groups from the tetra-*O*-alkylated intermediate by TFA resulted in the deprotected final product.

Based on the antibacterial tests, the compound was still not active against Gram-negative bacteria, actually it was less active than vancomycin against strains that were originally susceptible (MIC ≤ 0.5-2 μg/ml). Interestingly however, it proved to be more active than vancomycin against strains with reduced susceptibility/resistance to vancomycin. This might indicate that although the compound binds to the D-Ala-D-Ala termini with a lower affinity, by some other mechanism it is able to inhibit the vancomycin and teicoplanin resistant strains.

3.8. Synthesis of covalent dimers of teicoplanin and teicoplanin A_3-1

Starting from teicoplanin complex and TB (teicoplanin A_3-1) pseudoaglycon, a total of ten covalent dimers were prepared using two types of bis-isothiocyanate linkers. The synthesis of the first linker began with the di-*N*-alkylation of 1-aminodecane with 2-[2-(2-chloroethoxy)ethoxy]ethanol, then the two OH-groups of the resulting amino alcohol was converted to amine groups in three steps (*O*-tosylation, nucleophilic substitution with NaN_3, Staudinger reduction). By using carbon disulfide and di-*tert*-butyl-dicarbonate the previously obtained triamine was converted into the amphiphilic bis-isothiocyanate linker carrying a membrane anchor moiety with good yield. The other linker was obtained analogously to the first linker i.e. by the transformation of the OH-groups of hexaethyleneglycol and the amino groups of the resulting intermediate.

We prepared a total of six dimers with N-N orientation from TB and teicoplanin or their diethylaminopropyl amide. We reacted the monomers with a large excess of the linker, then after workup the appropriate monomer was added to the crude intermediate monomer. By following the same procedure, we prepared two TB and two teicoplanin dimers with N-C orientation. For this we had to protect the *N*-terminus (N-Boc- of *N*-trityl protecting groups) and transform the *C*-terminus. The identity and composition of multicomponent teicoplanin dimers was determined by HPLC-ESI-MS. In the case of the four symmetric dimers the main components were found in the same ratio in all mixtures. In the case of the two *N*-*C* dimers the number of components was much higher due to the asymmetry, however, based on the detected molecular weights, the two monomers of a particular dimer could be specified.

In the *in vitro* antibacterial tests, the activity of the dimers proved to be the same or lower than that of the parent compounds. The only exception was the case of the VanA *E. faecalis* strain, against which the N-N dimer of teicoplanin showed better activity than teicoplanin. Generally, the N-N dimers were more active than the N-C dimers, and the transformation of the *C*-terminus into

the diethylaminopropyl amide was beneficial. The linker with the *n*-decyl and tertiary amine function provided better activity than the linker without the anchoring unit. The two most active dimers were the N-N dimers of teicoplanin amide and TB-amide. These inhibited the growth of bacterial strains of the standard panel in the 4-8 μg/mL range.

4. Summary

During my PhD research I prepared semisynthetic analogues of two glycopeptide antibiotics, vancomycin and teicoplanin.

A simple, low-cost method was elaborated for the synthesis of teicoplanin pseudoaglycon (TC). As a continuation of a previous research in our department, some *N*-terminal 1,2,3-triazole derivatives of TC were prepared using the CuAAC reaction. Among these, the most active derivative proved to be the α-naphthyloxymethyl analogue. By introducing a tetraethyleneglycol linker into the side chain of the *n*-decyl triazole derivative, the obtained compound gained significant activity against influenza viruses, furthermore, its cytotoxicity decreased. By shortening the alkyl group, the cytotoxicity was lowered, however, the antiviral activity was also lost. Some *N*-terminal sulfonamides of TC were also prepared. Despite being notably more active against resistant strains than the parent compounds, the sulfonamides did not outperform the triazoles. The sulfonamides also displayed good anti-influenza virus activity. By transforming the *C*-terminus of the α-naphthyloxymethyl TC triazole derivative into an amide group containing a basic amine function, the antibacterial activity was successfully enhanced. Analogues that differ from the α-naphthyloxymethyl derivative not only in the structure of the *C*-terminus, but also in the number of carbohydrates on the peptide core were also synthesized. The activity of variants with two (TB) or three (TEI) carbohydrate moieties was about the same as that of the original triazole derivative, however, according to the literature, they might have better pharmacokinetic profiles.

By utilizing *N*,*N*'-disubstituted carbodiimides, the *N*-terminus of basic amide derivatives of TC and teicoplanin was transformed into a guanidino-group functionalized with lipophilic structural elements. Among these compounds the teicoplanin *n*-octyl derivative had excellent activity both against *Staphylococcus* and *Enterococcus* strains.

With the aim of producing selective antiviral compounds, the side chains of the most active and least toxic teicoplanin derivatives were attached to the *N*- or *C*-terminus of vancomycin aglycon hexapeptide by CuAAC reaction, sulfonamide formation or amide coupling. The antiviral activity and the acceptable selectivity index of the *N*-terminal triazole derivatives were maintained, while their antibacterial activity decreased to a negligible level.

With the aim of achieving activity against Gram-negative bacteria, a basic, amphiphilic compound was synthesized by reacylation and the attachment of aminoethyl groups to vancomycin aglycon hexapeptide. Although the product was more active against vancomycin resistant *Enterococcus faecalis* than vancomycin, it did not gain activity against Gram-negative bacteria.

Starting from teicoplanin and teicoplanin A_3-1 (TB) pseudoaglycone, some covalent dimers were synthesized using two types of bis-isothiocyanate linkers, in two orientations. The antibacterial activity of the dimers did not exceed that of the parent compounds.

5. Scientific publications related to the dissertation

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Subject: PhD Publikációs Lista

Candidate: Zsolt Szűcs
Neptun ID: ESJ7YN
Doctoral School: Doctoral School of Pharmacy

List of publications related to the dissertation

1. **Szűcs, Z.**, Ostorházi, E., Kicsák, M., Nagy, L., Borbás, A., Herczegh, P.: New semisynthetic teicoplanin derivatives have comparable in vitro activity to that of oritavancin against clinical isolates of VRE.
   J. Antibiot. 72 (7), 524-534, 2019.
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3. **Szűcs, Z.**, Bereczki, I., Csávás, M., Rőth, E., Borbás, A., Batta, G., Ostorházi, E., Szatmári, R., Herczegh, P.: Lipophilic teicoplanin pseudoaglycon derivatives are active against vancomycin- and teicoplanin-resistant enterococci.
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4. **Szűcs, Z.**, Csávás, M., Rőth, E., Borbás, A., Batta, G., Perret, F., Ostorházi, E., Szatmári, R., Vanderlinden, E., Naesens, L., Herczegh, P.: Synthesis and biological evaluation of lipophilic teicoplanin pseudoaglycon derivatives containing a substituted triazole function.
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6. Other scientific publications

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List of other publications

5. Tevyashova, A. N., Bychkova, E. N., Korolev, A. M., Isakova, E. B., Mirchink, E. P., Osterman, I. A., Erdei, R., **Szűcs, Z.**, Batta, G.: Synthesis and evaluation of biological activity for dual-acting antibiotics on the basis of azithromycin and glycopeptides.
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   DOI: http://dx.doi.org/10.1016/j.bmcl.2018.11.038
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   J. Antibiot. 72 (2), 114-117, 2018.
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   IF: 2.446

7. Csávás, M., Miskovics, A., **Szűcs, Z.**, Rőth, E., Nagy, Z. L., Bereczki, I., Herczeg, M., Batta, G., Nemes-Nikodém, É., Ostorházi, E., Rozgonyi, F., Borbás, A., Herczegh, P.: Synthesis and antibacterial evaluation of some teicoplanin pseudoaglycon derivatives containing alkyl- and arylthiosubstituted maleimides.
   J. Antibiot. 68 (9), 579-585, 2015.
   DOI: http://dx.doi.org/10.1038/ja.2015.33
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