

# Synthesis of Antiviral Perfluoroalkyl Derivatives of Teicoplanin and Vancomycin

Ilona Bereczki,<sup>[a]</sup> Magdolna Csávás,<sup>[a]</sup> Zsolt Szűcs,<sup>[a, b]</sup> Erzsébet Róth,<sup>[a]</sup> Gyula Batta,<sup>[c]</sup> Eszter Ostorházi,<sup>[d]</sup> Lieve Naesens,<sup>[e]</sup> Anikó Borbás,<sup>\*,[a]</sup> and Pál Herczegh<sup>\*,[a]</sup>

The limited scope of antiviral drugs and increasing problem of antiviral drug resistance represent a global health threat. Glycopeptide antibiotics and their lipophilic derivatives have emerged as relevant inhibitors of diverse viruses. Herein, we describe a new strategy for the synthesis of dual hydrophobic and lipophobic derivatives of glycopeptides to produce selective antiviral agents without membrane-disrupting activity. Perfluorobutyl and perfluorooctyl moieties were attached through linkers of different length to azido derivatives of

vancomycin aglycone and teicoplanin pseudoaglycone, and the new derivatives were evaluated against a diverse panel of viruses. The teicoplanin derivatives displayed strong anti-influenza virus activity at nontoxic concentrations. Some of the perfluoroalkylated glycopeptides were also active against a few other viruses such as herpes simplex virus or coronavirus. These data encourage further exploration of glycopeptide analogues for broad antiviral application.

## Introduction

Many biologically active small molecules contain one or more fluorine substituents, owing to the beneficial effect of fluorination on pharmacokinetic and pharmacodynamic properties.<sup>[1–7]</sup> The use of fluorine substituents in medicinal chemistry has continuously increased,<sup>[8–10]</sup> and currently more than 50% of blockbuster drugs are fluorinated. In these compounds, the presence of a few fluorine atoms strongly modifies the biological activity and chemical reactivity, while having relatively low impact on the physical properties.<sup>[11,12]</sup> On the other hand, the physical characteristics of perfluori-

nated compounds are very different from those of the hydrogen-containing analogues. Most importantly, perfluorination simultaneously enhances hydrophobicity and lipophobicity,<sup>[13,14]</sup> a unique characteristic that creates exceptional biomedical possibilities. Although the number of pharmacologically applicable molecules containing perfluoroalkyl substituents is currently still limited, polyfluorinated compounds have shown promise in several areas of medicinal chemistry.<sup>[15–17]</sup>

In recent years, we conducted a systematic study on the synthesis of lipophilic derivatives of the glycopeptide antibiotics vancomycin, teicoplanin and ristocetin, and this yielded several new antibiotics with promising antibacterial and antiviral activity.<sup>[18–22]</sup> We demonstrated that the high lipophilicity of the side chains (C<sub>8</sub>–C<sub>10</sub> alkyl groups) in these molecules is essential for antiviral activity against, among others, influenza virus. However, antiviral activity proved accompanied by high cytotoxicity, probably due to a membrane-disrupting effect of the highly lipophilic side chains.<sup>[22]</sup> In addition, we found that cytotoxicity was reduced by decreasing the overall lipophilicity of the compounds following incorporation of a tetra(ethylene glycol) linker between the peptide core and the lipophilic group.<sup>[22]</sup> Hence, we assumed that attaching perfluoroalkyl groups that are highly hydro- and lipophobic might confer antiviral activity without creating a membrane-disrupting effect. Namely, it has been shown that triphilic polymers bearing bulky and lipophobic perfluorinated blocks do not mix well with the hydrocarbon chains of lipids, explaining their low membrane partition coefficients.<sup>[23,24]</sup> This is the reason why fluorinated surfactants are non-cytolytic, that is, they are unable to solubilize membranes, as opposed to their hydrogenated counterparts.<sup>[25]</sup>

Herein, we report on the synthesis and antiviral plus antibacterial evaluation of perfluoroalkyl derivatives of vancomycin aglycone and teicoplanin pseudoaglycone.


[a] Dr. I. Bereczki, Dr. M. Csávás, Dr. Z. Szűcs, E. Róth, Prof. A. Borbás, Prof. P. Herczegh  
Department of Pharmaceutical Chemistry  
University of Debrecen  
Egyetem tér 1, 4032 Debrecen (Hungary)  
E-mail: borbas.aniko@pharm.unideb.hu  
herczeghp@gmail.com


[b] Dr. Z. Szűcs  
Doctoral School of Pharmaceutical Sciences  
University of Debrecen  
Egyetem tér 1, 4032 Debrecen (Hungary)

[c] Dr. G. Batta  
Department of Organic Chemistry  
University of Debrecen  
Egyetem tér 1, 4032 Debrecen (Hungary)

[d] Dr. E. Ostorházi  
Department of Medical Microbiology  
Semmelweis University  
Mária u. 41, 1085 Budapest (Hungary)

[e] Prof. L. Naesens  
Rega Institute for Medical Research  
KU Leuven  
3000 Leuven (Belgium)

 Supporting information for this article is available on the WWW under <https://doi.org/10.1002/cmdc.202000260>

 © 2020 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

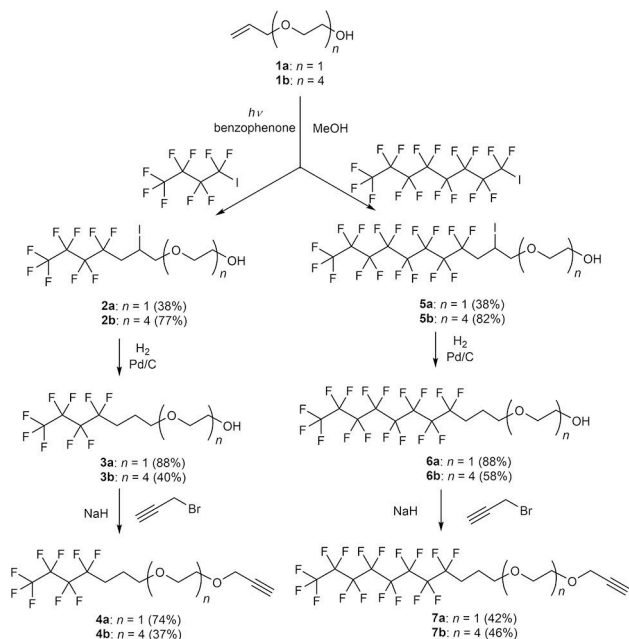
Although synthetic modification of glycopeptide antibiotics is increasingly recognized in the context of antiviral<sup>[26]</sup> and antibacterial<sup>[27]</sup> drug design, our study is the first to explore conjugation of glycopeptides with perfluoroalkyl groups.

## Results and Discussion

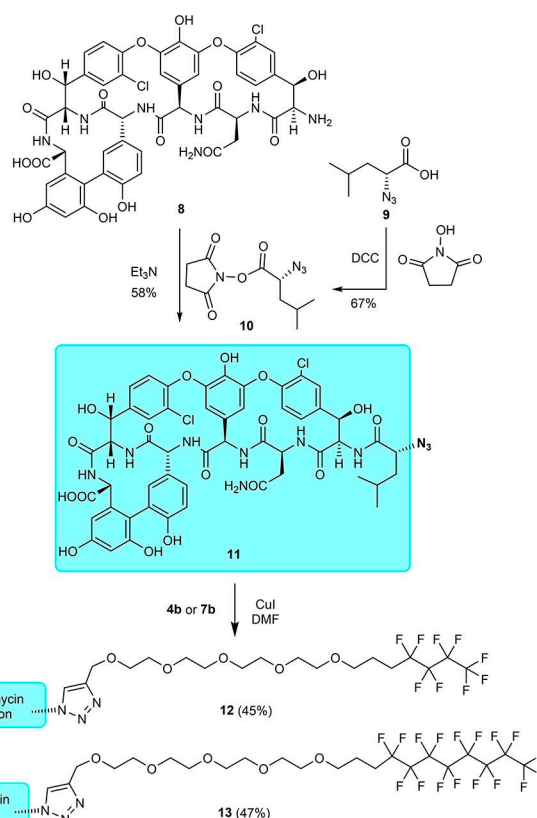
### Synthesis

Our recent results on semisynthetic lipoglycopeptides revealed that the type and length of the linkers significantly modifies the antiviral activity and cytotoxicity.<sup>[22]</sup> Herein, we have chosen the **1a** and **1b** allyl ethers of ethylene and tetra (ethylene glycol)s as linker chains between perfluoroalkyl substituents and the antibiotic molecules (Scheme 1). A light-promoted atom-transfer radical addition reaction<sup>[28]</sup> of the commercially available perfluorobutyl iodide and perfluorooctyl iodide onto the double bond of **1a** and **1b** resulted in **2a** and **2b**, as well as **5a** and **5b** in good yields. Attempted reductive removal of iodo substituent with  $\text{LiAlH}_4$  proceeded with low efficacy. Fortunately, catalytic hydrogenation of the iodo derivatives gave **3a** and **3b**, as well as **6a** and **6b** with moderate to high yields. Finally, these derivatives were reacted with propargyl bromide, respectively, to produce propargylated compounds **4a** and **4b** and **7a** and **7b** that are suitable for the azide alkyne cycloaddition click reaction.

For the derivatization of vancomycin aglycon, an N-terminal azido analogue **11** was prepared (Scheme 2). Vancomycin hexapeptide **8** obtained from vancomycin aglycone by Edman degradation<sup>[29]</sup> was acylated with D-azidovaline succinimide ester **10** prepared from D-azidovaline



**Scheme 1.** Assembly of the clickable perfluoroalkyl side chains **4a**, **4b**, **7a** and **7b**.



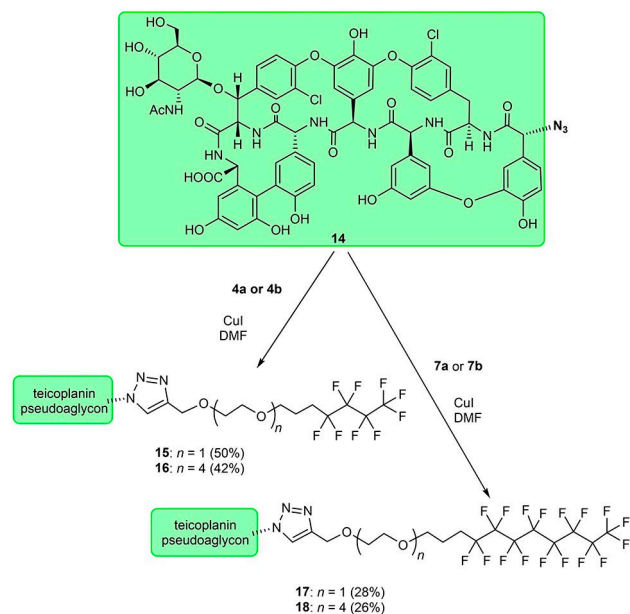
**Scheme 2.** Synthesis of vancomycin aglycone azide **11** and its conjugation with fluorinated side chains.

cine **9**.<sup>[30]</sup> A copper(I)-catalyzed 1,3-dipolar cycloaddition reaction of **4b** or **7b** with **11** resulted in perfluorobutyl and perfluorooctyl derivatives **12** and **13** of vancomycin aglycone.

Similar click reactions of azido derivative of teicoplanin pseudoaglycone **14**<sup>[18]</sup> with **4a**, **4b**, **7a**, or **7b** afforded perfluoroalkyl derivatives **15**, **16**, **17** and **18** with linker chains of different length (Scheme 3).

### Structure elucidation and testing oligomerization

In addition to NMR structure validation (see the Supporting Information, including  $^{13}\text{C}$  HSQC, HMBC,  $^{13}\text{C}$  and  $^{19}\text{F}$  spectra and spectral assignments) we tested compound **17** for possible oligomerization. Strong head to tail dimers are commonly found of glycopeptide antibiotics in aqueous solutions, that is co-operatively enhanced by ligand binding.<sup>[31–33]</sup> As **17** is not soluble in water, it was dissolved in MeOD for NMR diffusion experiments.<sup>[34]</sup> We used the internal mass standard method as described earlier.<sup>[35]</sup> TMS (tetramethylsilane, MW=88.2) and  $\beta$ -cyclodextrin ( $\beta$ -CD, MW=1135) were used alternatively. About 20 mg of sample **17** was dissolved in 500  $\mu\text{L}$  MeOD and measured at 300 K temperature. Spectra were recorded with 32 or 64 linear gradient steps and evaluated with topspin 2.1 software using inverse Laplace transformation to obtain diffusion domain.



**Scheme 3.** Attachment of fluorinated side chains of different length to teicoplanin pseudoaglycone.

These experiments yielded MW between 7–8 kDa when referenced to internal TMS. (Figure S1). However, in repeated measurements with ~3 mg of **17** dissolved in MeOD and referenced to internal  $\beta$ -CD, DOSY yielded only 2.4 kDa mass for **17**, that is closer to monomeric state (Figure S2). In control DOSY experiments of teicoplanin and vancomycin dissolved in  $[D_6]$ DMSO with  $\beta$ -CD mass reference, DOSY yielded the monomeric molecular masses as expected. Hence, we do not suppose the presence of oligomers in case of dilute MeOD solutions of **17**.

## Biological evaluation

Vancomycin aglycone derivatives **12** and **13** were inactive against various influenza strains and both were highly cytotoxic in MDCK cells (Table 1). Perfluorobutyl and perfluorooctyl derivatives **15**, **16** and **17** of teicoplanin pseudoaglycone displayed robust activity against influenza A and B virus with a favorable selectivity (i.e., ratio between cytotoxicity and activity). In contrast, the similar perfluorooctyl derivative **18** with a tetra(ethylene glycol) linker displayed high cytotoxicity without antiviral activity. Although this marked difference between vancomycin and teicoplanin derivatives may seem surprising, we previously demonstrated that even a slight difference in the peptide core can lead to very different antiviral properties.<sup>[36]</sup>

Besides, activity was noted against herpes simplex virus and vaccinia virus compounds (**15**, **16**, **17** and **18**), adenovirus (**15** and **17**) and coronavirus (**17** and **18**; Table 2). Two other sensitive viruses were respiratory syncytial virus ( $EC_{50}$  values: 9.9  $\mu$ M for **15**; 11  $\mu$ M for **16** and 4.6  $\mu$ M for **17**; MTS-based CPE assay in HeLa cells) and Zika virus ( $EC_{50}$  for **15**: 10  $\mu$ M; MTS-based CPE assay in Vero cells; Tables S1 and S2).

The broad activity of teicoplanin pseudoaglycone derivatives **15**, **16** and **17** against different viruses is consistent with our hypothesis that these derivatives may act by disrupting the viral endocytosis process, similarly to what we reported for a glycopeptide active against influenza virus.<sup>[37]</sup> Recently, it has been described that glycopeptide antibiotics like teicoplanin, dalbavancin, oritavancin and telavancin are able to prevent the host cell entry processes of Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV), which results also fit with our surmise.<sup>[38,39]</sup>

Finally, the antibacterial activity was evaluated on a panel of Gram-positive bacteria (Table 3). Vancomycin derivatives **12** and **13** displayed moderate activity. Perfluorooctyl derivatives **17** and **18** of teicoplanin pseudoaglycone were inactive, but perfluorobutyl compounds **15** and **16** had excellent antibacterial activity against sensitive and resistant staph-

**Table 1.** Cytotoxicity and anti-influenza virus activity in MDCK<sup>[a]</sup> cell cultures.

Compound	Cytotoxicity [ $\mu$ M]		Antiviral $EC_{50}$ <sup>[d]</sup> [ $\mu$ M]				Influenza B	
	MCC <sup>[b]</sup>	CC <sub>50</sub> <sup>[c]</sup>	A/H1 N1 CPE	MTS	A/H3 N2 CPE	MTS	CPE	MTS
<b>12</b>	42	4	> 100	> 100	> 100*	> 100*	> 100	> 100
<b>13</b>	0.8	0.8	> 100	> 100	> 100*	> 100*	> 100	> 100
<b>15</b>	100	> 100	7.7	7.2	2.3	1.9	8.9	11
<b>16</b>	100	97	5.6	1.6	2.3*	2.5*	5.6	6.5
<b>17</b>	100	44	6.8	8.6	1.2	1.6	4.0	3.4
<b>18</b>	–	4.2	–	> 100	–	> 100*	–	> 100
teicoplanin	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
<b>14</b>	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
vancomycin-HCl	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
zanamivir	> 100	> 100	1.5	3.1	20	9.0	2	1.7

[a] Madin Darby canine kidney cells. Virus strains: A/H1 N1: A/Ned/378/05; A/H3 N2: A/HK/7/87\* or A/Victoria/361/11; influenza B virus: B/Ned/537/05. [b] Minimum cytotoxic concentration, i.e., minimal compound concentration causing a microscopically detectable alteration in cell morphology. [c] 50% cytotoxic concentration based on the formazan-based MTS cell viability assay. [d] 50% effective concentration, or concentration producing 50% inhibition of virus-induced cytopathic effect, as determined by visual CPE scoring (left column), or by measuring cell viability with the MTS assay (right column).

**Table 2.** Cytotoxicity and antiviral activity in HEL<sup>[a]</sup> cell cultures.

Compound	Cytotoxicity CC <sub>50</sub> <sup>[b]</sup> [μM]	Antiviral EC <sub>50</sub> <sup>[c]</sup> [μM] HSV-1	HSV-1/TK <sup>-</sup>	HSV-2	Vaccinia	AdV-2	HCoV
15	> 100	54	39	2.0	10	42	> 100
16	> 100	33	41	25	48	> 100	> 100
17	> 100	16	16	2.2	7.9	60	40
18	> 100	9.8	19	14	17	> 100	4.9
cidofovir	> 250	2.4	4.7	1.0	10	6.4	–
acyclovir	> 250	2.4	146	0.05	> 250	–	–
alovudine	> 250	–	–	–	–	5.9	–

[a] HEL: human embryonic lung fibroblast cells. Viruses: herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2); a thymidine-kinase deficient (TK<sup>-</sup>) mutant of HSV-1; vaccinia virus; human adenovirus type 2 (AdV-2) and human coronavirus (HCoV) 229E. [b] 50% Cytotoxic concentration based on the formazan-based MTS cell viability assay. [c] 50% Effective concentration, based on measuring cell viability with the MTS assay.

**Table 3.** Antibacterial effects.

	TEI	VAN	MIC <sup>[a]</sup> [μg/mL]					
			12	13	15	16	17	18
<i>Bacillus subtilis</i> ATCC <sup>[a]</sup> 6633	0.5	0.5	32	16	0.5	2	128	4
<i>Staphylococcus aureus</i> MSSA <sup>[b]</sup> ATCC 29213	0.5	0.5	4	8	0.5	0.5	16	8
<i>S. aureus</i> MRSA <sup>[c]</sup> ATCC 33591	0.5	0.5	8	8	0.5	0.5	16	4
<i>Staphylococcus epidermidis</i> ATCC 35984 biofilm	2	2	8	16	0.5	0.5	16	4
<i>S. epidermidis</i> mecA <sup>[d]</sup>	16	4	8	8	0.5	0.5	256	8
<i>Enterococcus faecalis</i> ATCC 29212	2	1	8	4	0.5	1	256	16
<i>E. faecalis</i> 15376 VanA <sup>[e]</sup>	256	256	16	256	1	2	256	32
<i>E. faecalis</i> ATCC 51299 VanB <sup>[f]</sup>	4	128	16	32	4	1	256	32

[a] American Type Culture Collection. [b] Methicillin-sensitive *S. aureus*. [c] Methicillin-resistant *S. aureus*. [d] mecA gene expression in *Staphylococcus*. [e] vanA gene positive. [f] vanB gene positive. [g] Minimum inhibitory concentration. TEI: teicoplanin, VAN: vancomycin.

ylcocci and good activity against resistant enterococci having vanA and vanB genes.

## Conclusion

We have designed and synthesized the first members of fluoroglycopeptides, a novel type of glycopeptide antibiotic derivatives bearing perfluoroalkyl side chains. Such substituents are not only hydrophobic, but at the same time lipophobic endowing the antibiotic molecules with unique physicochemical properties that are worth exploring and exploiting from an antimicrobial point of view. As the lipophobic perfluoroalkyl blocks are known to have no membrane activity, low cytotoxicity of the perfluoroalkylated glycopeptides were expected. However, the vancomycin derivatives and one of the teicoplanin molecules showed cytotoxicity on canine kidney cells whereas they were inactive against influenza viruses. At the same time, three of the new teicoplanin derivatives displayed high activity against the influenza strains studied, two were active against human corona and adenoviruses, and all teicoplanins proved to be active against vaccinia and herpes viruses without showing cytotoxicity. Moreover, perfluorobutyl derivatives of teicoplanin pseudoaglycone displayed excellent antibacterial activity against a panel of Gram-positive bacteria.

We hope that these results can open a new way in finding more effective antivirals based on glycopeptide antibiotics.

## Experimental Section

### General information

Compounds **1b**,<sup>[40]</sup> **8**,<sup>[29]</sup> **9**<sup>[30]</sup> and **14**<sup>[18]</sup> were synthesized according to the literature. Compound **1a** was purchased from Sigma-Aldrich, nonafluoro-1-iodobutane from TCI and heptadecafluoro-1-iodooctane from Alfa Aesar. TLC was performed on Kieselgel 60 F<sub>254</sub> (Merck) with detection either by immersing into ammonium molybdate-sulfuric acid solution followed by heating or by using Pauly's reagent for detection. Flash column chromatography was performed using Silica gel 60 (Merck 0.040–0.063 mm). The photo-initiated reactions were carried out in a borosilicate vessel by irradiation with a Hg lamp giving maximum emission at 365 nm. The <sup>1</sup>H NMR (500, 400 and 360 MHz) <sup>13</sup>C NMR (125, 100 and 90 MHz) and 2D NMR spectra were recorded with a Bruker DRX-360, Bruker DRX-400 and Bruker Avance II 500 spectrometer at 298 or 300 K. For DOSY (Diffusion Ordered Spectroscopy) experiments, Bruker AVANCE-II, 500 MHz spectrometer was applied, with manufacturer's "ledbpgp2 s" pulse sequence. Chemical shifts are referenced to Me<sub>4</sub>Si (0.00 ppm for <sup>1</sup>H) and to the solvent residual signals. MALDI-TOF MS analyses of the compounds were carried out in the positive reflectron mode (20 kV) using a BIFLEX III mass spectrometer (Bruker) equipped with delayed-ion extraction. A nitrogen laser (337 nm, 3 ns pulse width, 106–107 W/cm<sup>2</sup>) operating at 4 Hz was applied to produce laser desorption. 2,5-Dihydroxybenzoic acid (DHB) was used as matrix and F<sub>3</sub>CCOONa as cationizing agent in DMF. ESI-QTOF MS measurements were carried out on a maXis II UHR ESI-QTOF MS instrument (Bruker), in positive ionization mode. The following parameters were applied for the electrospray ion source: capillary voltage: 3.5 kV; end plate offset: 500 V; nebulizer pressure: 0.8 bar; dry gas temperature: 200 °C and dry gas flow rate: 4.5 L/min. Constant background correction was applied for each spectrum, the background was recorded before each sample by



injecting the blank sample matrix (solvent). Na-formate calibrant was injected after each sample, which enabled internal calibration during data evaluation. Mass spectra were recorded by otocControl version 4.1 (build: 3.5, Bruker) and processed by Compass Data-Analysis version 4.4 (build: 200.55.2969). The antibacterial evaluations were carried out as it was described in our previous publication.<sup>[27b]</sup>

**2-((4,4,5,5,6,6,7,7,7-Nonafluoro-2-iodoheptyl)oxy)ethan-1-ol (2a)**

Nonafluoro-1-iodobutane (2.1 mL, 4.15 g, 12 mmol) and benzophenone (20 mg, 0.11 mmol) were added to a solution of 2-(allyloxy)ethan-1-ol (**1a**; 1.02 g, 10 mmol) in methanol (15 mL). Argon gas was bubbled through the solution and then irradiation occurred for 10 min. The solvent was evaporated, and the product was purified by flash column chromatography (hexane/acetone 8:2) to yield **2a** (1.7 g, 38%) as a colorless liquid.  $R_f$ =0.34 (hexane/acetone 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ =4.44–4.35 (m, 1H, CH), 3.83–3.59 (m, 6H, 3CH<sub>2</sub>), 3.13–2.94 (m, 1H, CH<sub>2</sub>), 2.84–2.64 (m, 1H, CH<sub>2</sub>), 2.12 ppm (s, 1H, OH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ =117.7, 106.7 (4 C, CF<sub>2</sub> and CF<sub>3</sub>), 75.8, 72.4, 61.8 (3 C, CH<sub>2</sub>), 37.8 (t, 1 C, CH<sub>2</sub>), 14.9 ppm (1 C, CHI); HRMS (ESI):  $m/z$  calcd for  $\text{C}_9\text{H}_{10}\text{F}_9\text{IO}_2 + \text{Na}^+$ : 470.9479 [ $M + \text{Na}$ ]<sup>+</sup>; found: 470.9474.

**16,16,17,17,18,18,19,19,19-Nonafluoro-14-iodo-3,6,9,12-tetraoxanonadecan-1-ol (2b)**

Nonafluoro-1-iodobutane (0.944 mL, 1.9 g, 5.5 mmol) and benzophenone (10 mg, 0.055 mmol) were added to a solution of 3,6,9,12-tetraoxapentadec-14-en-1-ol (**1b**; 1.17 g, 5 mmol) in methanol (12 mL). Argon gas was bubbled through the solution and then irradiation occurred for 10 min. The solvent was evaporated, and the product was purified by flash column chromatography (hexane/acetone 7:3) to yield **2b** (2.09 g, 77%) as a colorless liquid.  $R_f$ =0.29 (hexane/acetone 7:3);  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ):  $\delta$ =4.41–4.31 (m, 1H, CH), 3.84–3.56 (m, 18H, 9CH<sub>2</sub>), 3.20–3.01 (m, 1H, CH<sub>2</sub>), 2.93–2.85 (m, 1H, OH), 2.77–2.57 ppm (m, 1H, CH<sub>2</sub>);  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$ =76.2, 72.6, 70.7, 70.65, 70.6, 70.5, 70.4, 61.7 (9 C, CH<sub>2</sub>), 37.4 (t, 1 C, CH<sub>2</sub>), 14.5 ppm (1 C, CHI); HRMS (ESI):  $m/z$  calcd for  $\text{C}_{15}\text{H}_{22}\text{F}_9\text{IO}_5 + \text{Na}^+$ : 603.0266 [ $M + \text{Na}$ ]<sup>+</sup>; found: 603.0260.

**2-((4,4,5,5,6,6,7,7,7-Nonafluoroheptyl)oxy)ethan-1-ol (3a)**

To the solution of **2a** (0.896 g, 2 mmol) in methanol (15 mL) 10% palladium on activated charcoal (270 mg) and  $\text{NaHCO}_3$  (420 mg, 5 mmol) were added. The reaction mixture was stirred overnight under  $\text{H}_2$  atmosphere, then filtered through Celite, and the solvent was evaporated. The residue was dissolved in dichloromethane (50 mL), and the solution was washed with distilled water (10 mL) two times, dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was evaporated in vacuum. The product was purified by flash column chromatography (hexane/acetone 8:2) to yield **3a** (571 mg, 88%) as a colorless liquid.  $R_f$ =0.50 (hexane/acetone 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ =3.75 (s, 2H, CH<sub>2</sub>), 3.62–3.53 (m, 4H, 2CH<sub>2</sub>), 2.32–2.11 (m, 3H, CH<sub>2</sub>, OH), 1.98–1.86 ppm (m, 2H, CH<sub>2</sub>);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ =72.2, 69.7, 61.9 (3 C, CH<sub>2</sub>), 27.9 (t, 1 C, CH<sub>2</sub>), 20.9 ppm (1 C, CH<sub>2</sub>).

**16,16,17,17,18,18,19,19,19-Nonafluoro-3,6,9,12-tetraoxanonadecan-1-ol (3b)**

$\text{LiAlH}_4$  (304 mg, 8 mmol) was added under argon to a solution of **2b** (2.32 g, 4 mmol) in abs. THF (20 mL), and the reaction mixture

was stirred overnight. Then 10%  $\text{Na}_2\text{SO}_4$  solution (5 mL) was added, and the mixture was stirred for 30 min. After filtration through Celite, the solvent was evaporated, and the product was purified by flash column chromatography (hexane/acetone 7:3) to yield **3b** (728 mg, 40%) as a colorless liquid.  $R_f$ =0.40 (hexane/acetone 7:3);  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ):  $\delta$ =3.77–3.52 (m, 18H, 9CH<sub>2</sub>), 2.28–2.10 (m, 2H, CH<sub>2</sub>), 1.95–1.83 ppm (m, 2H, CH<sub>2</sub>);  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$ =72.7, 70.7, 70.6, 70.4, 70.3, 69.8, 61.8 (9 C, CH<sub>2</sub>), 27.9 (t, 1 C, CH<sub>2</sub>), 20.8 ppm (1 C, CH<sub>2</sub>); HRMS (ESI):  $m/z$  calcd for  $\text{C}_{15}\text{H}_{23}\text{F}_9\text{O}_5 + \text{Na}^+$ : 477.1299 [ $M + \text{Na}$ ]<sup>+</sup>; found: 477.1293.

**2-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-2-iodoundecyl)oxy)ethan-1-ol (5a)**

Heptadecafluoro-1-iodooctane (3.17 mL, 6.55 g, 12 mmol) and benzophenone (20 mg, 0.11 mmol) were added to a solution of 2-(allyloxy)ethan-1-ol (**1a**; 1.02 g, 10 mmol) in methanol (15 mL). Argon gas was bubbled through the solution and then irradiation occurred for 10 min. The solvent was evaporated, and the product was purified by flash column chromatography (hexane/acetone 8:2) to yield **5a** (2.07 g, 38%) as a colorless liquid.  $R_f$ =0.43 (hexane/acetone 7:3);  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ):  $\delta$ =4.46–4.33 (m, 1H, CH), 3.83–3.61 (m, 6H, 3CH<sub>2</sub>), 3.16–2.91 (m, 1H, CH<sub>2</sub>), 2.87–2.62 (m, 1H, CH<sub>2</sub>), 2.28–2.14 ppm (m, 1H, OH);  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$ =117.9, 111.2 (CF<sub>2</sub> and CF<sub>3</sub>), 75.8, 72.4, 61.8 (3 C, CH<sub>2</sub>), 37.9 (t, 1 C, CH<sub>2</sub>), 15.0 ppm (1 C, CHI); HRMS (ESI):  $m/z$  calcd for  $\text{C}_{13}\text{H}_{10}\text{F}_{17}\text{IO}_2 + \text{Na}^+$ : 670.9352 [ $M + \text{Na}$ ]<sup>+</sup>; found: 670.9346.

**16,16,17,17,18,18,19,19,20,20,21,21,22,22,23,23,23-Heptadecafluoro-14-iodo-3,6,9,12-tetraoxatricosan-1-ol (5b)**

Heptadecafluoro-1-iodooctane (1.46 mL, 3.0 g, 5.5 mmol) and benzophenone (10 mg, 0.055 mmol) were added to a solution of 3,6,9,12-tetraoxapentadec-14-en-1-ol (**1b**; 1.17 g, 5 mmol) in methanol (12 mL). Argon gas was bubbled through the solution and then irradiation occurred for 10 min. The solvent was evaporated, and the product was purified by flash column chromatography (hexane/acetone 7:3) to yield **5b** (3.2 g, 82%) as a colorless liquid.  $R_f$ =0.40 (hexane/acetone 7:3);  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ):  $\delta$ =4.42–4.32 (m, 1H, CH), 3.85–3.56 (m, 18H, 9CH<sub>2</sub>), 3.20–2.91 (m, 2H, CH<sub>2</sub>, OH), 2.78–2.58 ppm (m, 1H, CH<sub>2</sub>);  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ ):  $\delta$ =117.8, 114.3, 111.2, 110.8 (8 C, CF<sub>2</sub>, CF<sub>3</sub>), 76.2, 72.7, 70.7, 70.66, 70.6, 70.5, 70.3, 61.7 (9 C, CH<sub>2</sub>), 37.5 (t, 1 C, CH<sub>2</sub>), 14.5 ppm (1 C, CHI); HRMS (ESI):  $m/z$  calcd for  $\text{C}_{19}\text{H}_{22}\text{F}_{17}\text{IO}_5 + \text{Na}^+$ : 803.0138 [ $M + \text{Na}$ ]<sup>+</sup>; found: 803.0133.

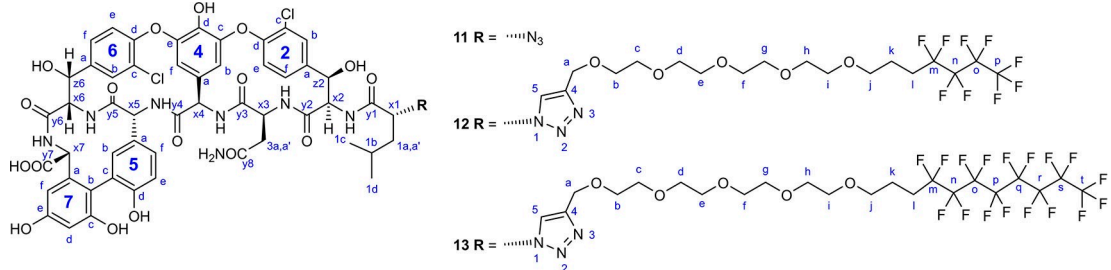
**2-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl)oxy)ethan-1-ol (6a)**

To a solution of **5a** (1.296 g, 2 mmol) in methanol (15 mL) 10% palladium on activated charcoal (270 mg) and  $\text{NaHCO}_3$  (420 mg, 5 mmol) were added. The reaction mixture was stirred overnight under  $\text{H}_2$  atmosphere, then filtered through Celite, and the solvent was evaporated. The residue was dissolved in dichloromethane (50 mL) and the solution was washed with distilled water (10 mL) two times, dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was evaporated in vacuum. The product was purified by flash column chromatography (hexane/acetone 8:2) to yield **6a** (922 mg, 88%) as a colorless liquid.  $R_f$ =0.58 (hexane/acetone 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ =3.78–3.72 (m, 2H, CH<sub>2</sub>), 3.61–3.53 (m, 4H, 2CH<sub>2</sub>), 2.29–2.04 (m, 3H, CH<sub>2</sub>, OH), 1.96–1.86 ppm (m, 2H, CH<sub>2</sub>);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ =118.7, 115.9, 110.9 (8 C, CF<sub>2</sub>, CF<sub>3</sub>); 72.2, 69.8, 61.9 (3 C, CH<sub>2</sub>), 28.1 (t, 1 C, CH<sub>2</sub>), 20.9 ppm (1 C, CH<sub>2</sub>); HRMS (ESI):  $m/z$  calcd for  $\text{C}_{13}\text{H}_{11}\text{F}_{17}\text{O}_2 + \text{Na}^+$ : 545.0385 [ $M + \text{Na}$ ]<sup>+</sup>; found: 545.0380.

Table 4. NMR data of vancomycin derivatives.

	11 <sup>1</sup> H	<sup>13</sup> C	12 <sup>1</sup> H	<sup>13</sup> C	13 <sup>1</sup> H
y1	–	177.2113	–	173.99	–
y8 (Asp)	–	173.9445	–	171.2	–
y2	–	172.0452	–	169.9	–
y3	–	171.4567	–	169.09	–
y4	–	171.3606	–	169.02	–
y5	–	169.1608	–	168.25	–
y7	–	n.d.	–	166.35	–
y6	–	n.d.	–	166.27	–
7e	–	157.5295	–	157.03	–
7c	–	156.6308	–	155.36	–
5d	–	155.5733	–	154.75	–
2d	–	151.3203	–	150.02	–
4e	–	150.7161	–	148.4	–
4c	–	149.3844	–	147.45	–
6d	–	148.395	–	147.16	–
6a	–	141.2641	–	143.63	–
2a	–	139.7893	–	142.25	–
7a	–	138.83	–	139.28	–
5b	7.09	136.83	7.22	135.81	7.23
4d	–	135.07	–	133.6	–
4a	–	129.33	–	128.42	–
2b	7.2	129.91	7.42	128.24	7.4
6b	7.56	128.57	7.89	127.28	7.88
6f	7.56	128.57	7.46	126.94	7.47
2c	–	128.77	–	126.51	–
2f	7.22	128.18	7.52	126.94	7.48
5a	–	127.16	–	125.81	–
6c	–	126.82	–	125.64	–
5f	6.87	127	6.75	124.51	6.72
2e	n.d.	n.d.	7.23	124.09	7.25
6e	n.d.	n.d.	7.23	122.74	7.24
5c	–	123.31	–	122.36	–
7b	–	119.11	–	117.21	–
5e	6.82	118.44	6.68	115.62	6.69
4f	5.49	106.59	5.6	106.82	5.57
7f	6.38	108.63	n.d.	n.d.	6.6
4b	5.26	105.23	5.21	104.12	5.21
7d	6.36	103.3	6.27	101.23	6.29
z6	5.18	72.76	5.18	71.01	5.15
z2	5.3	72.24	5.12	70.72	5.15
x6	4.09	63.7	4.17	61.52	4.18
x1	3.81	61.54	5.73	60.67	5.76
x2	4.33	60.43	4.73	58.99	4.73
x7	4.42	55.28	4.34	58.99	4.33
x4	5.96	55.28	5.7	54.41	5.71
x5	4.72	52.72	4.48	53.39	4.48
x3	n.d.	n.d.	4.33	50.75	4.35
1a,a'	2.36	39.26	1.92/2.04	39.96	1.91, 2.03
3a,a'	n.d.	n.d.	2.16/2.58	36.26	2.89
1b	1.75	24.64	1.23	23.96	1.18
1c	n.d.	n.d.	0.9	21.04	0.82
1d	n.d.	n.d.	0.83	22.15	0.89
side chain					
triazole CH (5)			8.18	122.61	8.2
triazole C (4)			–	118.32	–
OCH <sub>2</sub> (a)			4.55	63.15	4.52
OCH <sub>2</sub>			3.52	69.41	3.5
OCH <sub>2</sub>			3.54	69.36	3.5
OCH <sub>2</sub>			3.52	69.11	3.5

Table 4. continued

					
11	<sup>1</sup> H	<sup>13</sup> C	12	<sup>1</sup> H	
			<sup>13</sup> C	13	
			<sup>1</sup> H		
OCH <sub>2</sub>			3.58	68.62	3.56
CH <sub>2</sub> (l)			3.5	68.11	3.48
CH <sub>2</sub> (k)			2.29	26.45	2.26
			1.77	19.92	1.75
n.d.: ■■■not determined OK?■■■.					

### 16,16,17,17,18,18,19,19,20,20,21,21,22,22,23,23-Heptadecafluoro-3,6,9,12-tetraoxatricosan-1-ol (6b)

LiAlH<sub>4</sub> (304 mg, 8 mmol) was added under argon to a solution of **5b** (3.12 g, 4 mmol) in abs. THF (20 mL), and the reaction mixture was stirred overnight. Then 10% Na<sub>2</sub>SO<sub>4</sub> solution (5 mL) was added and the mixture was stirred for 30 min. After filtration through Celite, the solvent was evaporated, and the product was purified by flash column chromatography (hexane/acetone 7:3) to yield **6b** (1.52 g, 58%) as a colorless liquid. *R*<sub>f</sub> = 0.30 (hexane/acetone 7:3); <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>): δ = 3.76–3.51 (m, 18H, 9CH<sub>2</sub>), 2.28–2.10 (m, 2H, CH<sub>2</sub>), 1.95–1.83 ppm (m, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (90 MHz, CDCl<sub>3</sub>): δ = 121.5, 118.8, 114.3, 110.8, 108.2 (8 C, CF<sub>2</sub>, CF<sub>3</sub>), 72.7, 70.6, 70.58, 70.3, 70.2, 69.7, 61.7 (9 C, CH<sub>2</sub>), 27.9 (t, 1 C, CH<sub>2</sub>), 20.7 ppm (1 C, CH<sub>2</sub>); HRMS (ESI): *m/z* calcd for C<sub>19</sub>H<sub>23</sub>F<sub>17</sub>O<sub>5</sub> + Na<sup>+</sup>: 677.1172 [*M* + Na]<sup>+</sup>; found: 677.1166.

### General procedure for propargylation (4a, 4b, 7a and 7b)

NaH (60% dispersion in mineral oil; 2 mmol) was washed with hexane, abs. THF (10 mL) was added and **3a**, **3b**, **6a** or **6b** (1 mmol) was dissolved in it. After 30 min of stirring, propargyl bromide (80% solution in toluene; 1.2 mmol) was added, and the reaction mixture was stirred for 3 h. Then ethyl acetate (5 mL) and methanol (1 mL) were added to the mixture, and it was stirred for 15 min. The solvent was evaporated, the residue was dissolved in dichloromethane and the solution was washed with distilled water (3x15 mL). The organic phase was dried on anhydrous Na<sub>2</sub>SO<sub>4</sub>, then it was filtered and evaporated in vacuum. The product was purified by flash column chromatography (hexane/acetone 8:2) to yield **4a**, **4b**, **7a** or **7b** as yellowish liquids.

### 1,1,1,2,2,3,3,4,4-Nonafluoro-7-(2-(prop-2-yn-1-yloxy)ethoxy)heptane (4a)

Yield 267 mg (74%); *R*<sub>f</sub> = 0.58 (hexane/acetone 7:3); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 4.21 (d, *J* = 2.4 Hz, 2H, CH<sub>2</sub> propargyl), 3.73–3.67 (m, 2H, CH<sub>2</sub>), 3.66–3.61 (m, 2H, CH<sub>2</sub>), 3.56 (t, *J* = 6.1 Hz, 2H, CH<sub>2</sub>), 2.43 (t, *J* = 2.4 Hz, 1H, CH propargyl), 2.29–2.12 (m, 2H, CH<sub>2</sub>), 1.95–1.85 ppm (m, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 79.6 (1 C, C<sub>q</sub> propargyl), 74.6 (1 C, CH propargyl), 70.2, 69.9, 69.2 (3 C, CH<sub>2</sub>), 58.5 (1 C, CH<sub>2</sub> propargyl) 28.0 (t, 1 C, CH<sub>2</sub>), 20.8 ppm (1 C, CH<sub>2</sub>).

### 20,20,21,21,22,22,23,23-Nonafluoro-4,7,10,13,16-pentaoxaatriacos-1-yne (4b)

Yield 180 mg (37%); *R*<sub>f</sub> = 0.46 (hexane/acetone 7:3); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 4.20 (d, *J* = 2.4 Hz, 2H, CH<sub>2</sub> propargyl), 3.74–3.57 (m, 16H, CH<sub>2</sub>), 3.55 (t, *J* = 6.1 Hz, 2H, CH<sub>2</sub>), 2.43 (t, *J* =

2.4 Hz, 1H, CH propargyl), 2.27–2.10 (m, 2H, CH<sub>2</sub>), 1.93–1.83 ppm (m, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 74.6 (1 C, CH propargyl), 70.7, 70.5, 70.3, 69.8, 69.2 (9 C, CH<sub>2</sub>), 58.5 (1 C, CH<sub>2</sub> propargyl) 27.9 (t, 1 C, CH<sub>2</sub>), 20.8 ppm (1 C, CH<sub>2</sub>); HRMS (ESI): *m/z* calcd for C<sub>18</sub>H<sub>25</sub>F<sub>9</sub>O<sub>5</sub> + Na<sup>+</sup>: 515.1456 [*M* + Na]<sup>+</sup>; found: 515.1451.

### 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluoro-11-(2-(prop-2-yn-1-yloxy)ethoxy)undecane (7a)

Yield 234 mg (42%); *R*<sub>f</sub> = 0.64 (hexane/acetone 7:3); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 4.21 (d, *J* = 2.4 Hz, 2H, CH<sub>2</sub> propargyl), 3.73–3.67 (m, 2H, CH<sub>2</sub>), 3.66–3.61 (m, 2H, CH<sub>2</sub>), 3.56 (t, *J* = 6.1 Hz, 2H, CH<sub>2</sub>), 2.43 (t, *J* = 2.4 Hz, 1H, CH propargyl), 2.29–2.12 (m, 2H, CH<sub>2</sub>), 1.95–1.85 ppm (m, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 118.7, 116.2, 111.0 (8 C, CF<sub>2</sub>, CF<sub>3</sub>), 79.7 (1 C, C<sub>q</sub> propargyl), 74.6 (1 C, CH propargyl), 70.2, 69.9, 69.2 (3 C, CH<sub>2</sub>), 58.6 (1 C, CH<sub>2</sub> propargyl) 28.1 (t, 1 C, CH<sub>2</sub>), 20.9 ppm (1 C, CH<sub>2</sub>); HRMS (ESI): *m/z* calcd for C<sub>16</sub>H<sub>13</sub>F<sub>17</sub>O<sub>2</sub> + Na<sup>+</sup>: 583.0542 [*M* + Na]<sup>+</sup>; found: 583.0535.

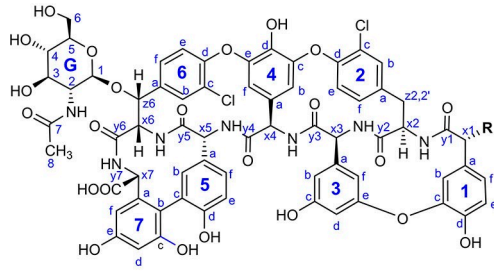
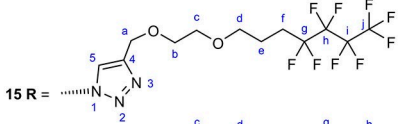
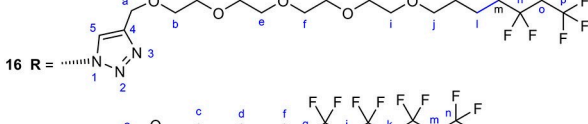
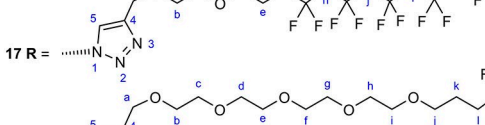

### 20,20,21,21,22,22,23,23,24,24,25,25,26,26,27,27-Heptadecafluoro-4,7,10,13,16-pentaoxaheptacos-1-yne (7b)

Yield 318 mg (46%); *R*<sub>f</sub> = 0.42 (hexane/acetone 7:3); Compound **7b** was reacted with the azido glycopeptide derivatives without characterization by NMR; HRMS (ESI): *m/z* calcd for C<sub>22</sub>H<sub>25</sub>F<sub>17</sub>O<sub>5</sub> + Na<sup>+</sup>: 715.1328 [*M* + Na]<sup>+</sup>; found: 715.1323.

### 2,5-Dioxopyrrolidin-1-yl (R)-2-azido-4-methylpentanoate (10)

2-Azido-4-methylpentanoic acid (**9**; 1.256 g, 8 mmol) and *N*-hydroxysuccinimide (1.013 g, 8.8 mmol) were dissolved in abs. dichloromethane (50 mL) and after cooling in an ice bath, dicyclohexylcarbodiimide (1.76 g, 8.5 mmol) was added. The reaction mixture was stirred overnight at room temperature, then filtered through Celite and the solvent was evaporated in vacuum, and co-evaporated with chloroform (2x50 mL) two times. Then it was dissolved in acetonitrile, filtered through Celite and after evaporation the product was purified by flash column chromatography (hexane/ethyl acetate 8:2) to yield **10** (1.1 g, 67%). *R*<sub>f</sub> = (hexane/ethyl acetate 8:2); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 4.17 (dd, *J* = 8.8, 5.8 Hz, 2H, CH), 2.86 (s, 4H, CH<sub>2</sub>), 1.99–1.77 (m, 3H, CH, CH<sub>2</sub>), 1.01 ppm (dd, *J* = 9.5, 6.4 Hz, 6H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 168.7, 166.9 (3 C, C=O), 58.3 (1 C, CH), 39.9 (1 C, CH<sub>2</sub>), 25.6 (2 C, CH<sub>2</sub>) 24.9, 22.7, 21.5 ppm (3 C, CH, CH<sub>3</sub>); MALDI-TOF MS: [*M* + Na]<sup>+</sup> = 277.204 *m/z*. Calcd (C<sub>10</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>Na) 277.091 *m/z*.

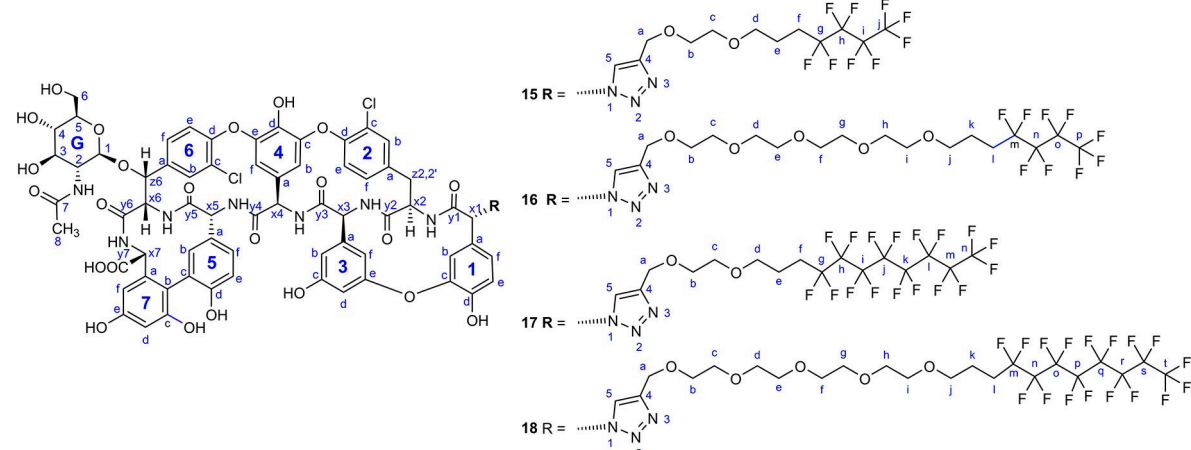
Table 5. NMR data of teicoplanin derivatives.

	15	<sup>13</sup> C	16	<sup>13</sup> C	17	<sup>13</sup> C	18	<sup>13</sup> C
y1	–	174.36	–	173.79	–	n.d.	–	173.47
y7	–	170.02	–	169.90	–	169.67	–	169.94
y4	–	169.68	–	169.44	–	169.67	–	169.37
y2	–	169.36	–	169.25	–	169.17	–	169.19
y5	–	169.00	–	168.87	–	168.58	–	168.83
y3	–	168.33	–	168.22	–	167.16	–	168.17
y6	–	167.46	–	167.30	–	166.53	–	167.30
C=O(NAc) G7	–	165.94	–	165.58	–	n.d.	–	165.59
3c	–	158.56	–	158.46	–	159.90	–	158.45
7e	–	157.75	–	157.65	–	158.51	–	157.60
3e	–	156.87	–	156.75	–	158.24	–	156.73
7c	–	155.75	–	155.62	–	157.05	–	155.67
5d	–	155.61	–	155.49	–	155.95	–	155.44
2d	–	151.16	–	151.07	–	155.95	–	151.04
6d	–	149.21	–	149.10	–	151.15	–	149.08
4c	–	148.96	–	148.83	–	149.53	–	148.77
4e	–	148.02	–	147.93	–	148.13	–	147.91
1d	–	147.49	–	147.42	–	147.60	–	147.40
triazole-q (4)	–	143.78	–	143.76	–	143.59	–	143.75
6a	–	142.74	–	142.60	–	142.19	–	142.61
1c	–	140.94	–	140.89	–	139.09	–	140.83
3a	–	139.49	–	139.68	–	138.17	–	139.37
7a	–	138.62	–	138.64	–	135.18	–	138.60
5b	7.12	136.1	7.12	136.01	7.17, 7.09	136.3	7.11	135.97
2a	–	135.41	–	135.3	–	135.18	–	135.30
4d	–	134.43	–	134.74	–	n.d.	–	134.31
1a	–	n.d.	–	134.36	–	n.d.	–	n.d.
2b	7.21	131	7.2	130.91	7.15	130.24	7.21	130.94
2f	7.94	130.6	7.89	130.46	7.72	131.25	7.92	130.44
4a	–	127.22	–	127.13	–	126.81	–	128.6
6c	–	126.7	–	126.59	–	126.71	–	128
6f	7.26	127.81	7.28	127.8	7.25	127.74	7.27	128
6b	7.86	128.49	7.87	128.35	7.81	128.29	7.87	128.37
2c	–	125.43	–	125.33	–	n.d.	–	127.13
5a	–	125.43	–	125.33	–	n.d.	–	126.59
5f	6.67	125.12	6.66	125.29	6.65	125.02	6.66	125.32
1f	6.9	125.59	6.9	125.48	7.04	124.33	6.9	125.48
2e	7.19	124.84	7.18	124.72	7.08	127.15	7.19	124.73
6e	6.99	119.0	6.96	118.94	7.24	123	7.27	123.05
triazole-CH (5)	7.74	123.98	7.71	123.81	7.7	123.88	7.72	123.78
5c	–	122.17	–	122.19	–	122.2	–	122.06
1e	7.26	123.24	7.25	123.06	6.89	118.61	7.05	119.37
7b	–	117.82	–	117.71	–	117.87	–	117.71
1b	7.04	119.49	7.04	119.39	6.94	119.6	6.97	118.91
5e	6.65	116.45	6.64	116.38	6.65	116.32	6.64	116.37
3b	6.34	110.03	6.34	109.97	6.32	109.53	6.34	109.97
4b	5.5	108.05	5.56	107.92	5.54	107.65	5.56	108
7f	6.5	107.86	6.52	107.92	6.53	107.73	6.48	107.68
3d	6.38	105.1	6.37	104.97	6.34	104.17	6.37	104.99
4f	5.1	104.59	5.1	104.46	5.09	104.26	5.1	104.47
3f	6.55	104.02	6.55	103.84	6.57	103.39	6.55	103.85



Table 5. continued



	15	<sup>13</sup> C	16	<sup>13</sup> C	17	<sup>13</sup> C	18	<sup>13</sup> C
7d	6.32	101.68	6.3	101.51	6.31	101.52	6.3	101.56
G1	4.38	99.27	4.4	98.73	4.37	99.42	4.42	98.57
G5	3.1	76.79	3.11	76.77	3.09	76.44	3.11	76.77
G3	5.4	76.14	5.45	75.58	5.35	76.2	5.44	75.43
G4	3.39	73.38	3.4	73.4	3.4	72.89	3.41	73.4
z6	3.22	70.02	3.25	69.97	3.26	69.13	3.23	70.05
x6	4.16	60.94	4.15	60.88	4.2	60.46	4.14	60.87
G6	3.62	60.25	3.6	60.29	3.39	60.1	3.6	60.38
x3	5.4	58.31	5.41	58.21	5.36	58.41	5.41	58.17
x1	4.33	59.28	4.33	59.22	4.28	59.08	4.36	58.9
x7	7.12	64.04	7.09	64.03	7.06	64.18	7.1	63.98
G2	3.52	55.8	3.52	55.9	3.59	55.23	3.51	55.98
x4	5.65	54.67	5.63	54.65	5.6	54.27	5.64	54.64
x2	4.87	55.46	4.89	55.37	4.97	55	4.88	55.38
x5	4.37	53.61	4.37	53.53	4.38	53.22	4.36	53.54
z2,2'			n.d.	n.d.			3.32, 2.92	36.18
Side chain								
OCH <sub>2</sub> (a)	4.45	63.29	4.45	63.25	4.45	63.04	4.45	63.23
OCH <sub>2</sub>	3.48	69.34	3.48	69.32	3.48	69.07	3.5	69.67
OCH <sub>2</sub>	3.51	68.9	3.51	69.08	3.51	68.62	3.5	69.38
OCH <sub>2</sub>	3.44	68.48	3.44	68.5	3.44	68.24	3.46	68.48
							3.5	68.39
CH <sub>2</sub> (e)	1.73	20.25			1.73	20.26		
CH <sub>2</sub> (f)	2.24	26.76			2.23	26.87		
CH <sub>2</sub> (k)			1.76	20.23			1.76	20.24
CH <sub>2</sub> (l)			2.23	26.86			2.28	26.85

## Compound 11

To the solution of vancomycin aglycone hexapeptide (**8**; 1.5 g, 1.48 mmol) in abs. *N,N*-dimethylformamide (50 mL) triethylamine (206  $\mu$ L, 1.48 mmol) and **10** (753 mg, 2.96 mmol) were added. The reaction mixture was stirred for 3 h, the solvent was evaporated, and the product was purified by flash column chromatography (acetonitrile/water 9:1) to yield **11** (986 mg, 58%) as a yellow powder.  $R_f$ =0.34 (acetonitrile/water 9:1); NMR data can be found in Table 4.; MALDI-TOF MS:  $[M+Na]^+$ =1177.089  $m/z$ . Calcd ( $C_{52}H_{48}Cl_2N_{10}O_{17}Na$ ) 1177.247  $m/z$ .

General procedure for click reaction (**12**, **13**, **15**, **16**, **17** and **18**)

To the solution of azide (**11** or **14**; 0.1 mmol) in *N,N*-dimethylformamide (2 mL) triethylamine (14  $\mu$ L, 0.1 mmol), alkyne (**4a**, **4b**, **7a** or **7b**; 0.12 mmol) and Cu<sup>I</sup> iodide (10 mg) were added. The reaction mixture was stirred overnight, then the solvent was evaporated and the product was purified by flash column

chromatography (toluene/methanol 7:3→6:4→1:1 for **12** and **13** or acetonitrile/water 9:1 for **15**, **16**, **17**, and **18**) to yield **12**, **13**, **15**, **16**, **17** or **18**. After lyophilization all of the products were yellow solid foams.

**12**: Yield 71 mg (45%);  $R_f$ =0.53 (toluene/methanol 6:4); NMR data can be found in Table 4; HRMS (ESI):  $m/z$  calcd for  $C_{70}H_{73}Cl_2F_9N_{10}O_{22}+Na^+$ : 1669.4032  $[M+Na]^+$ ; found: 1669.4020.

**13**: Yield 87 mg (47%);  $R_f$ =0.58 (toluene/methanol 6:4); NMR data can be found in Table 4; HRMS (ESI):  $m/z$  calcd for  $C_{74}H_{73}Cl_2F_{17}N_{10}O_{22}+Na^+$ : 1869.3904  $[M+Na]^+$ ; found: 1869.3873.

**15**: Yield 90 mg (50%);  $R_f$ =0.49 (acetonitrile/water 85:15); NMR data can be found in Table 5; HRMS (ESI):  $m/z$  calcd for  $C_{78}H_{69}Cl_2F_9N_{10}O_{25}+Na^+$ : 1809.3566  $[M+Na]^+$ ; found: 1809.3549.

**16**: Yield 80 mg (42%);  $R_f$ =0.14 (acetonitrile/water 9:1); NMR data can be found in Table 5.; HRMS (ESI):  $m/z$  calcd for  $C_{84}H_{80}Cl_2F_9N_{10}O_{28}Na+Na^+$ : 1963.4554  $[M-H+2Na]^+$ ; found: 1963.4150.

17: Yield 56 mg (28%);  $R_f$  = 0.50 (acetonitrile/water 85:15); NMR data can be found in Table 5; HRMS (ESI):  $m/z$  calcd for  $C_{82}H_{67}Cl_2F_{17}N_{10}O_{25}Na_2 + Na^+$ : 2053.3078  $[M-2H+3Na]^+$ ; found: 2053.3078.

18: Yield 52 mg (26%);  $R_f$  = 0.23 (acetonitrile/water 9:1); NMR data can be found in Table 5; HRMS (ESI):  $m/z$  calcd for  $C_{88}H_{81}Cl_2F_{17}N_{10}O_{28} + Na^+$ : 2141.4225  $[M+Na]^+$ ; found: 2141.4199.

## Antiviral procedures

The CPE reduction assay for influenza virus was described in full detail in previous publications.<sup>[41]</sup> The virus strains were: A/PR/8/34 (A/H1 N1); A/Virginia/ATCC3/2009 (A/H1 N1pdm); A/HK/7/87 (A/H3 N2); B/Ned/537/05; and B/HK/5/72. On day 0, Madin-Darby canine kidney (MDCK) cells in 96-well plates were infected with influenza virus at a multiplicity of infection (MOI) of 0.0004 plaque forming units (PFU) per cell. After three days incubation at 35 °C, virus-induced CPE and compound cytotoxicity were scored by microscopy, after which the data were confirmed by formazan-based MTS cell viability assay (CellTiter 96® AQueous One Solution Cell Proliferation Assay from Promega). The antiviral effect was expressed as the compound concentration producing 50% inhibition of the virus-induced CPE ( $EC_{50}$ ). Compound cytotoxicity was expressed as the compound concentration causing minimal changes in cell morphology (MCC), and 50% cytotoxic concentration ( $CC_{50}$ ) based on MTS assay.<sup>[42]</sup>

Inhibitory effect against human coronavirus 229E was determined using a CPE reduction assay in human embryonic lung fibroblast (HEL) 299 cells, described in full detail elsewhere.<sup>[43]</sup> We also reported the detailed methodology for the other DNA and RNA viruses in the test panel.<sup>[44]</sup> The  $EC_{50}$ ,  $CC_{50}$  and MCC values were calculated as described.<sup>[42]</sup>

## Acknowledgements

This work was supported by the European Regional Development Fund under the projects GINOP-2.3.2-15-2016-00044, GINOP-2.3.2-15-2016-00008 and GINOP-2.3.3-15-2016-00004 and by the European Social Fund under the project EFOP-3.6.3-VEKOP-16-2017-00009. This research was also funded by the National Research, Development and Innovation Office of Hungary (K119509).

## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** antiviral • coronavirus • glycopeptide antibiotic • influenza virus • perfluoroalkyl

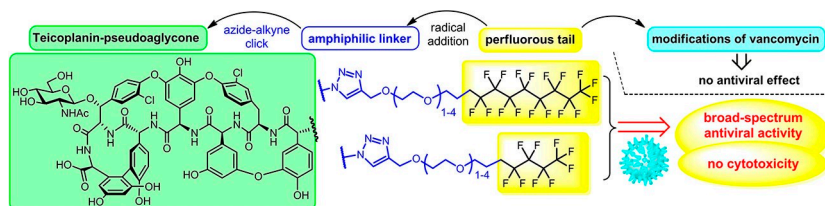
- [1] H. J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643.
- [2] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.
- [3] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.
- [4] W. K. Hagmann, *J. Med. Chem.* **2008**, *51*(15), 4359–4369.
- [5] I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Blackwell Publishing Ltd **2009**.
- [6] V. Gouverneur, K. Müller, *Fluorine in Pharmaceutical and Medicinal Chemistry*, Imperial College Press, Singapore **2012**.

- [7] G. Haufe, F. Leroux, *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals: Progress in Fluorine Science Series*, 1st ed., Academic Press **2018**.
- [8] J. Wang, M. Sanchez-Rosell, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.
- [9] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.
- [10] H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797–11819.
- [11] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.
- [12] N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880.
- [13] J.-P. Bégue, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley **2008**.
- [14] B. Jeffries, Z. Wang, H. R. Felstead, J.-Y. Le Questel, J. S. Scott, E. Chiarpain, J. Graton, B. Linclau, *J. Med. Chem.* **2020**, *63*, 1002–1031.
- [15] E. Prchalová, O. Štěpánek, S. Smrček, M. Kotora, *Future Med. Chem.* **2014**, *6*, 1201–1229.
- [16] V. I. Saloutin, V. I. Il'enkol, A. Piterikh, V. G. Platonov, V. Kiseleva, K. I. Pashkevich, *Pharm. Chem. J.* **1986**, *20*, 501–504. Translated from *Khim.-Farm. Zh.* **1986**, *20*(7), 847–851.
- [17] M. Bassetto, S. Ferla, F. Pertusati, *Future Med. Chem.* **2015**, *7*(4), 527–546.
- [18] G. Pintér, G. Batta, S. Kéki, A. Mándi, I. Komáromi, K. Takács-Novák, F. Sztaricskai, E. Róth, E. Ostorházi, F. Rozgonyi, L. Naesens, P. Herczegh, *J. Med. Chem.* **2009**, *52*(19), 6053–6061.
- [19] Z. Szűcs, I. Bereczki, M. Csávás, E. Róth, A. Borbás, G. Batta, E. Ostorházi, R. Szatmári, P. Herczegh, *J. Antibiot.* **2017**, *70*, 664–670.
- [20] Z. Szűcs, M. Csávás, E. Róth, A. Borbás, G. Batta, F. Perret, E. Ostorházi, R. Szatmári, E. Vanderlinden, L. Naesens, P. Herczegh, *J. Antibiot.* **2017**, *70*, 152–157.
- [21] Z. Szűcs, E. Ostorházi, M. Kicsák, L. Nagy, A. Borbás, P. Herczegh, *J. Antibiot.* **2019**, *72*, 524–534.
- [22] Z. Szűcs, V. Kelemen, S. L. Thai, M. Csávás, E. Róth, G. Batta, A. Stevaert, E. Vanderlinden, L. Naesens, P. Herczegh, A. Borbás, *Eur. J. Med. Chem.* **2018**, *157*, 1017–1030.
- [23] E. Amadoa, J. Kressler, *Soft Matter* **2011**, *7*, 7144–7149.
- [24] E. Amado, A. Blumeand, J. Kressler, *React. Funct. Polym.* **2009**, *69*, 450–456.
- [25] K.-H. Park, C. Berrier, F. Lebaupain, B. Pucci, J.-L. Popot, A. Ghazi, F. Zito, *Biochem. J.* **2007**, *403*, 183–187.
- [26] a) P. Colson, D. Raoult, *Int. J. Antimicrob. Agents* **2016**, *48*, 349–352; b) G. Li, E. De Clercq, *Nat. Rev. Drug Discovery* **2020**, *19*, 149–150.
- [27] Recent examples for semisynthetic glycopeptides with high antibacterial activity: a) V. Yarlagaadda, P. Akkapeddi, G. B. Manjunath, J. Haldar, *J. Med. Chem.* **2014**, *57*, 4558–4568; b) Z. Szűcs, I. Bereczki, M. Csávás, E. Róth, A. Borbás, G. Batta, E. Ostorházi, R. Szatmári, P. Herczegh, *J. Antibiot.* **2017**, *70*, 664–670; c) Z. Szűcs, E. Ostorházi, M. Kicsák, L. Nagy, A. Borbás, P. Herczegh, *J. Antibiot.* **2019**, *72*, 524–534; d) V. Vimberg, R. Gazak, Z. Szűcs, A. Borbás, P. Herczegh, J. P. Cavanagh, L. Zieglerova, J. Závora, V. Adámková, G. Balikova Novotna, *J. Antibiot.* **2019**, *72*, 114–117.
- [28] R. Beniazza, R. Atkinson, C. Absalon, F. Castet, S. A. Denisov, N. D. McClenaghan, D. Lastécouères, J.-M. Vincent, *Adv. Synth. Catal.* **2016**, *358*, 2949–2961.
- [29] P. M. Booth, D. J. M. Stone, D. H. Williams, *J. Chem. Soc. Chem. Commun.* **1987**, 1694–1695.
- [30] I. E. Valverde, A. Bauman, C. A. Kluba, S. Vomstein, M. A. Walter, T. L. Mindt, *Angew. Chem. Int. Ed.* **2013**, *52*(34), 8957–8960.
- [31] G. Batta, F. Sztaricskai, K. E. Kövér, C. Rüdel, T. F. Berdnikova, *J. Antibiot.* **1991**, *44*, 1208–1221.
- [32] W. G. Prowse, A. D. Kline, M. A. Skelton, R. J. Loncharich, *Biochemistry* **1995**, *34*, 9632–9644.
- [33] N. E. Allen, T. I. Nicas, *Microbiol. Rev.* **2003**, *26*, 511–532.
- [34] P. Stilbs, *Prog. Nucl. Magn. Reson. Spectrosc.* **1987**, *19*, 1–45.
- [35] L. Orosz, G. Batta, S. Kéki, M. Nagy, G. Deák, M. Zsuga, *Carbohydr. Res.* **2007**, *342*, 1323–1328.
- [36] I. Bereczki, A. Mándi, E. Róth, A. Borbás, Á. Fizil, I. Komáromi, A. Sipos, T. Kurtán, G. Batta, E. Ostorházi, F. Rozgonyi, E. Vanderlinden, L. Naesens, F. Sztaricskai, P. Herczegh, *Eur. J. Med. Chem.* **2015**, *94*, 73–86.
- [37] E. Vanderlinden, E. Vanstreels, E. Boons, W. ter Veer, A. Huckriede, D. Daelemans, A. Van Lommel, E. Roth, F. Sztaricskai, P. Herczegh, L. Naesens, *J. Virol.* **2012**, *86*, 9416–9431.
- [38] N. Zhou, T. Pan, J. Zhang, Q. Li, X. Zhang, C. Bai, F. Huang, T. Peng, J. Zhang, C. Liu, L. Tao, H. Zhang, *J. Biol. Chem.* **2016**, *291*, 9218–9232.

- [39] Y. Wang, R. Cui, G. Li, Q. Gao, S. Yuan, R. Altmeyer, G. Zou, *Antiviral Res.* **2016**, *125*, 1–7.
- [40] a) D. Voerman, M. Schluck, J. Weiden, B. Joosten, L. J. Eggermont, T. van den Eijnde, B. Ignacio, A. Cambi, C. G. Figdor, P. H. J. Kouwer, M. Verdoes, R. Hammink, A. E. Rowan, *Biomacromolecules* **2019**, *20*, 2587–2597; b) C. Zona, G. D'Orazio, B. La Ferla, *Synlett* **2013**, *24*, 709–712.
- [41] G. Cihan-Üstündag, M. Zopun, E. Vanderlinden, E. Ozkirimli, L. Persoons, G. Capan, L. Naesens, *Bioorg. Med. Chem.* **2020**, *28*, 115130.
- [42] P. Vrijens, S. Noppen, T. Boogaerts, E. Vanstreels, R. Ronca, P. Chiodelli, M. Laporte, E. Vanderlinden, S. Liekens, A. Stevaert, L. Naesens, *J. Gen. Virol.* **2019**, *100*, 583–601.
- [43] Ç. B. Apaydin, N. Cesur, A. Stevaert, L. Naesens, Z. Cesur, *Arch. Pharm. (Weinheim)* **2019**, *352*:e1800330.
- [44] D. Rogolino, M. Carcelli, A. Bacchi, C. Compari, L. Contardi, E. Fiscaro, A. Gatti, M. Sechi, A. Stevaert, L. Naesens, *J. Inorg. Biochem.* **2015**, *150*, 9–17.

---

Manuscript received: April 22, 2020  
Revised manuscript received: June 28, 2020  
Accepted manuscript online: July 11, 2020  
Version of record online: ■■■, ■■■■



**Plan F:** Perfluoroalkylated blocks were incorporated into azido glycopeptide derivatives of vancomycin and teicoplanin. The teicoplanin derivatives displayed strong antiviral activity against a diverse panel of viruses at nontoxic concentrations. The vanco-

mycin derivatives showed cytotoxicity, while being inactive against influenza viruses. Perfluorobutylated teicoplanins displayed excellent antibacterial activity against a panel of Gram-positive bacteria.

Dr. I. Bereczki, Dr. M. Csávás, Dr. Z. Szűcs, E. Róth, Dr. G. Batta, Dr. E. Ostorházi, Prof. L. Naesens, Prof. A. Borbás\*, Prof. P. Herczegh\*

1 – 12

## Synthesis of Antiviral Perfluoroalkyl Derivatives of Teicoplanin and Vancomycin



Synthesis of antiviral perfluoroalkyl derivatives of teicoplanin and vancomycin (Borbás, Herczegh et al. @Degyetem @semmelweishu @LeuvenU)

Share your work on social media! *ChemMedChem* has added Twitter as a means to promote your article. Twitter is an online microblogging service that enables its users to send and read short messages and media, known as tweets. Please check the pre-written tweet in the galley proofs for accuracy. If you, your team, or institution have a Twitter account, please include its handle @username. Please use hashtags only for the most important keywords, such as #catalysis, #nanoparticles, or #protein design. The ToC picture and a link to your article will be added automatically, so the **tweet text must not exceed 250 characters**. This tweet will be posted on the journal's Twitter account (follow us @ChemMedChem) upon publication of your article in its final (possibly unpaginated) form. We recommend you to re-tweet it to alert more researchers about your publication, or to point it out to your institution's social media team.

## ORCID (Open Researcher and Contributor ID)

Please check that the ORCID identifiers listed below are correct. We encourage all authors to provide an ORCID identifier for each coauthor. ORCID is a registry that provides researchers with a unique digital identifier. Some funding agencies recommend or even require the inclusion of ORCID IDs in all published articles, and authors should consult their funding agency guidelines for details. Registration is easy and free; for further information, see <http://orcid.org/>.

Dr. Ilona Bereczki  
 Dr. Magdolna Csávás  
 Dr. Zsolt Szűcs  
 Erzsébet Róth  
 Dr. Gyula Batta  
 Dr. Eszter Ostorházi  
 Prof. Lieve Naesens  
 Prof. Anikó Borbás <http://orcid.org/0000-0001-8462-4547>  
 Prof. Pál Herczegh