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1,2,3-Triazolium-based cationic amphipathic peptoid oligomers mimicking antimicrobial helical peptides

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Abstract: Amphipathic cationic peptoids (*N*-substituted glycine oligomers) represent a promising class of antimicrobial peptide mimics. The aim of this study is to explore the potential of the triazolium group as a cationic moiety and helix inducer to develop potent antimicrobial helical peptoids. We report here the first solid-phase synthesis of peptoid oligomers incorporating 1,2,3-triazolium-type side chains, and their evaluation against *Escherichia coli, Enterococcus faecalis* and *Staphylococcus aureus*. Several triazolium-based oligomers, even of short length, selectively kill bacteria over mammalian cells. SEM visualization of *S. aureus* cells treated with a dodecamer and a hexamer reveals severe cell membrane damages and suggests that the longer oligomer acts by pore formation.

The increasing emergence of multidrug-resistant pathogenic bacterial strains has let to intense research on alternative strategies to overcome microbial infections. Part of the innate immune system, antimicrobial peptides (AMPs) have gained increased attention due to their broad spectrum activity against bacteria, fungi and parasites.[1] Besides, their main mechanism of action by bacterial cell membrane disruption implies low emergence of resistance. However their exploitation as therapeutics was hampered by unsuitable toxicity and pharmacokinetics.[2] Peptidomimetics exhibiting the mechanism of action of AMPs with enhanced proteolytic stability have been widely explored during the last decade.[3] Many of these mimetics have been designed to exhibit the cationic amphipathic helical structure of native AMPs, which is the key determinant of their activity.[4] Among them, peptoids (*N*-substituted glycine oligomers)[5] represent a promising class of AMP mimics.[4e, 6]Peptoids possess desirable advantages such as protease stability, cost-effective synthesis, and a great potential for diversity.[7] The Barron group showed that the threefold periodicity of the polyproline type-I -like helix (PPI) of α-peptoids[8] enabled mimicry of the magainin helical structure.[4e] The amphipathic helix was built by periodic incorporation of a cationic side chain every three residues, the remaining positions being occupied by the aromatic α-chiral (*S*)-phenylethyl side chain which helps the formation of helix and provides hydrophobic helical faces (Figure 1a,b,c). The dodecamer (*N*Lys-*N*spe-*N*spe)$_4$ showed excellent broad spectrum antibacterial activities, but also displayed potent cytotoxicity towards carcinoma cells.[9] Parameters that may have an

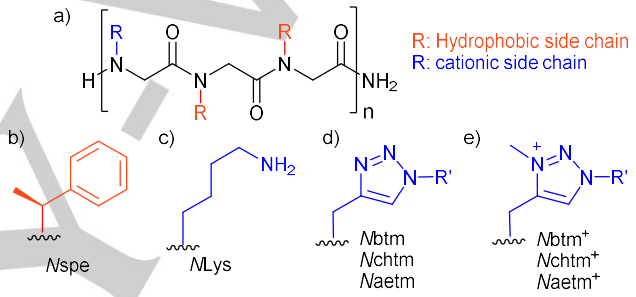


Figure 1.a) Generic structure of cationic amphiphilic peptoids; Side chain structure of *N*-glycine residues: b) *N*spe for (S)-*N*-(1-phenylethyl)glycine; c) *N*Lys for*N*-(4-aminobutyl)glycine; d) *N*btm for *N*-(1-benzyl-1,2,3-triazolylmethyl)glycine, *N*chtmfor *N*-(1-cyclohexylmethyl-1,2,3-triazolylmethyl)glycine and *N*aetm for *N*-(1-(2-aminoethyl)-1,2,3-triazolylmethyl)glycine; e) *N*btm$^+$ for *N*-(1-benzyl-3-methyl-1,2,3-triazolium methyl)glycine, *N*chtm$^+$ for *N*-(1-cyclohexylmethyl-3-methyl-1,2,3-triazolium methyl)glycine and*N*aetm$^+$ for *N*-(1-(2-aminoethyl)-3-methyl-1,2,3-triazolium methyl)glycine.

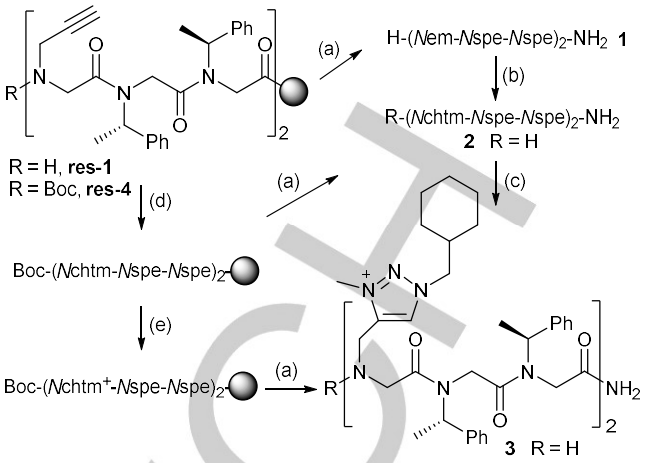
influence on activities (oligomer length, charge, hydrophobicity, chirality, secondary structure and side chain nature), the mode of action of these peptidomimetics and their selectivity for bacteria *vs* mammalian cells have been scrutinized over the last ten years.[6,10]A number of descriptors have been identified to predict potency of designed linear peptoids.[11] Cyclisation has been shown to increase the membrane activity resulting in superior *in vitro* bacterial growth inhibition.[12] Despite the huge number of amphipathic cationic peptoid oligomers studied, the chemical diversity of the cationic pendant groups is limited to date to positively charged proteinogenic side chain equivalents *i.e.* ammonium, guanidinium, and imidazolium moieties. These side chains bring the positive charge but do not exert any role on the folding into amphipathic helix. The use of cationic side chain involved in the stabilization of the helix may provide short amphiphilic oligomers with interesting antimicrobial properties. The PPI-like helix can be generated using side chains which stabilize the *cis* conformation of the backbone amides through steric and/or electronic interactions.[8,13] The 1,2,3-triazolium-type side chain exhibits a strong *cis*-directing effect thanks to an efficient $n\rightarrow\pi^*_{Ar}$ electronic interaction.[14] This positively-charged side chain should enable to target bacterial membrane while

promoting helical folding of peptoid oligomer. 1,2,3-Triazolium salts have been extensively studied for application as ionic liquids, catalysts or receptors but their implication in substances of biological interest was by far less explored than its 1,2,3-triazole parent.[15]

In this communication, we report on the synthesis and the evaluation of peptoids incorporating triazolium-type side chains (Figure 1). Our aim was to explore the potential of the triazolium as cationic pendant group and structuring element to develop potent AMP mimetics. Based on the rational design of amphipathic cationic peptoid structure,[4e,6] oligomers comprising trimer repeats with two consecutive bulky α-chiral *spe* side chains and one cationic 1,2,3-triazolium-type side chain were designed. The best way for the multivalent formation of 1,2,3-triazolium groups was initially assessed by synthesising the model hexamer H-(*N*chtm$^+$-*N*spe-*N*spe)$_2$-NH$_2$ **3** in solution or on support (Scheme 1).

First, peptoid **1** carrying site-specifically located *spe* side chains and propargyl side chains (*em*) as triazolium precursors, wasprepared by standard microwave-assisted solid-phase submonomer strategy.[6] Triazole formation in solution was achieved by using a standard Cu-Catalysed Azide-Alkyne (CuAAC) reaction protocol. Using cyclohexylmethyl azide, the conversion of the alkynyl functions into triazolyl was achieved, yielding hexapeptoid **2** in 52% yield. Conversion of the triazoles into triazoliums was tested using a well-established protocol (Scheme 1).[16] A complex mixture of compounds was obtained likely due to the presence of the primary amide and the unprotected terminal-amine group. This result prompted us to develop a new strategy consisting in forming the triazolium moiety directly on the resin after a prerequisite protection of the *N*-terminal amine. Therefore, the supported peptoid **res-1** was protected with a Boc group, sensitive to the resin cleavage conditions. The multiple CuAAC reaction was then performed on supported peptoid **res-4** using copper iodide, Hünig's base and ascorbic acid.[17] Thereafter, triazolium formation was studied on support. On the basis of previous work, methyl iodide was chosen as alkylating reagent at various concentrations in diverse solvents and at different temperature. Most of the time, only one methylation occurred providing a complex mixture of compounds. Complete conversion of triazole into triazolium was finally achieved by exposing the resin to pure methyl iodide at 45°C during 5h. Then, hexapeptoid **3** was cleaved from support and efficiently obtained. Using this approach, three series of oligomers were generated with various substituents on triazole/triazolium: an aminoethyl, a cyclohexylmethyl and a benzyl for series A, B and C, respectively (Table 1 and ESI for details). This library includes oligomers with a sequence length of 6, 9 and 12 residues and an overall positive charge ranging from 0 to +8.

The antibacterial activity of the designed amphiphiles was assessed against both Gram-negative bacteria (two strains of *Escherichia coli)* and Gram-positive bacteria (*Enterococcus*



Scheme 1. Synthetic access to 1,2,3-triazolium-based model hexamer **3**. Key: (a) TFA/TIS/H_2O; (b) cyclohexylmethyl azide, $CuSO_4$, ascorbic acid, H_2O/*t*BuOH, 12h; (c) MeI, CH_3CN, 70°C; (d) cyclohexylmethyl azide, CuI, DIPEA, ascorbic acid, DMF/pyridine, 18h; (e) MeI, 45°C; Abbreviations: *N*em for *N*-(ethynylmethyl)glycine.

Table 1. Antibacterial activities and selectivity of triazole- and triazolium-based cationic amphipathic peptoids.

Series/Nbr	*Peptoid sequence*	*MW*[a]	*charge*	MIC [μM] [b]				HC_{10}/HC_{50}[c]	CV[d]	SR[e]
				*E. coli**	*E. coli***	*E. faecalis*	*S. aureus*	[μM]	(%)	
ref	H-(*N*Lys-*N*spe-*N*spe)$_4$-NH$_2$	1819	4	3.5[6]	14-24[6]	-	-	21/100[6]	-	-
A/**5**	H-(*N*aetm$^+$-*N*spe-*N*spe)$_2$-NH$_2$	1249	4	>200.0	>200.0	>200.0	>200.0	-	-	-
A/**6**	H-(*N*aetm$^+$-*N*spe-*N*spe)$_3$-NH$_2$	1864	6	25.0	100.0	50.0	50.0	>200/>200	100±9.2	>4
A/**7**	H-(*N*aetm$^+$-*N*spe-*N*spe)$_4$-NH$_2$	2480	8	11.5±1.0	50.0	6.3	6.3	>200/>200	100±11.8	>31
A/**8**	H-(*N*aetm-*N*spe-*N*spe)$_4$-NH$_2$	2031	4	6.3	12.5	11.5±1.0	10.4±1.3	>100/>200	6±6.3	>9
B/**2**	H-(*N*chtm-*N*spe-*N*spe)$_2$-NH$_2$	1130	0	> 200.0	> 200.0	> 200.0	> 200.0	-	-	-
B/**3**	H-(*N*chtm$^+$-*N*spe-*N*spe)$_2$-NH$_2$	1355	2	50.0	50.0	6.3	3.1	>200/>200	100±9.8	>64
B/**9**	H-(*N*chtm$^+$-*N*spe-*N*spe)$_3$-NH$_2$	2023	3	25.0	25.0	1.8±0.3	1.6	50/>75	7±6.0	31
C/**10**	H-(*N*btm$^+$-*N*spe-*N*spe)$_3$-NH$_2$	2053	3	12.5	12.5	1.6	1.6	>50/>100	7±5.9	>31
	Melittin[f]	2847	6	6.3(4-16)[18]	6.3	6.3(1-8)[19]	3.1(0.5-4)[19]	-/7[20]	-	-

[a] Molecular weight including triazolium counterions. [b] Minimum inhibitory concentration (MIC) was determined as the lowest concentration of peptide that inhibited bacteria growth of *Escherichia coli* *JM109 and **ATCC® 25922™, *Enterococcus faecalis* ATCC® 29212™, *Staphylococcus aureus* CIP 6525. A minimum of three independent experiments of the assay were conducted, and two technical replicates were used in each experiment for each bacterium, peptoid and concentration. [c] Haemolytic concentrations at which 10% and 50% haemolysis are observed. Assays were performed in triplicates. [d] Cell viability (CV): average percentage of viable HeLa cells after peptoid exposition at 100 μM during 24h (MTT assay). Data are presented as the means ±SEM of three independent experiments. [e] Selectivity ratio SR = $HC_{10}/MIC_{S.aureus}$; [f] Honey bee peptide GIGAVLKVLTTGLPALISWIKRKRQQ …

faecalis and *Staphylococcus aureus*) (Table 1). Selectivity for bacterial over mammalian cells was assessed by testing the haemolytic activities on human red blood cells (hRBC) and the toxicity on HeLa cell. In the series A, antimicrobial potency exponentially increased with oligomer length as usually observed for cationic amphiphilic peptoids.[6,10] The hexamer **5** has no effect on bacterial strains whereas the dodecamer **7** exhibits high antibacterial activities particularly on Gram-positive bacteria. In contrast with previous studies, no increase of haemolytic activity was observed for longer oligomers (**6** versus **7**). By contrast with the triazolium, the triazole may not exert any marked influence on the peptoid main-chain for adoption of a PPI-like helical conformation. However, the dodecamer **8** bearing uncharged triazole moieties, was found to have a broad spectrum activity with potency similar to that of the reference sequence against *E. coli*.[6] Accordingly, in this first series, the incorporation of a triazolium group in between the peptoid backbone and the ammonium cationic moiety did not show any beneficial effect on the MIC values. But these triazolium-based peptoids were less haemolytic and toxic than their triazole precursors and the reference sequence (**7** versus **8** and **ref**). In the series B and C, the net positive charge of the oligomers arises exclusively from the triazolium groups. As expected compound **2** with the uncharged triazoles was inactive on bacteria. However, quaternisation of the two triazoles resulted in the cationic amphiphile **3** with unprecedented antibacterial activities for a linear peptoid of this length. Indeed, MIC of 6.3 and 3.1 μM were measured against *E. faecalis* and *S. aureus,* respectively. It is important to note that in the course of antimicrobial peptoids design, short oligomers were often poorly active except those incorporating the dehydroabietyl moiety or a long alkyl tail.[21] The potency of peptoid **3** may be due to the structuring effect of the triazolium.[14,16] Preliminary CD study on this series showed that peptoids **2**, **3** and **9** present the characteristic CD signature of the PPI-like helix of peptoids with two minima at 203 and 220 nm (Figure 2).[8] The lower band intensity for triazole-based hexapeptoid **2** compared to the triazolium-based hexapeptoid **3** is indicative of the helical structure stabilisation by the triazoliums. Besides, a similar CD signature was observed for the hexamer **3** and the nonamer **9** suggesting that the short oligomer has already good helical integrity which may explain its good activity.

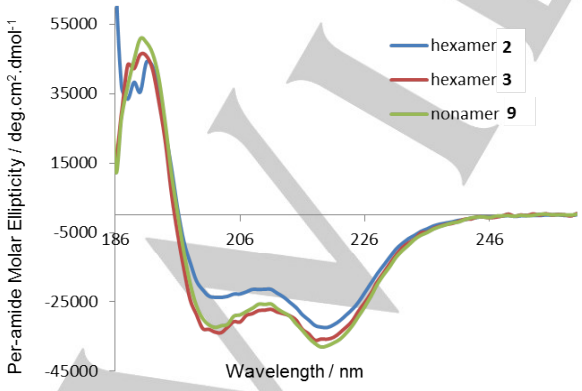


Figure 2. Circular dichroism (CD) spectra of series B oligomers at 500 μM in MeOH.

The lengthened peptoid **9** showed a two- or three-fold decrease in the MIC value for all bacteria. Regrettably, this nonamer proved more haemolytic (HC_{10} 50 μM) than the hexamer **3** but the selectivity ratio remained very acceptable. Lastly, the influence of additional aromatic group was studied by comparison of nonamers **9** and **10**. It is usually noticed in AMP mimetics design that hydrophobic aromatic groups help at improving antibacterial activity but were often detrimental to the specificity.[4,6,10] The nonamer **10** exhibits the best activities over the panel of bacterial strains studied and was surprisingly slightly less haemolytic than nonamer **9** with a selectivity ratio SR greater than 31.

As for AMPs, studies have provided evidence that amphipathic cationic peptoids act by bacterial membrane disruption,[6,12b,22] however additional modes of action are not excluded.[18c,23] Changes in membrane morphology of *S. aureus* bacteria upon treatment with dodecamer **7**, the longest peptoid from the A series and the short hexamer **3** from the B series, were visualized using Scanning Electron Microscopy (Figure 3).

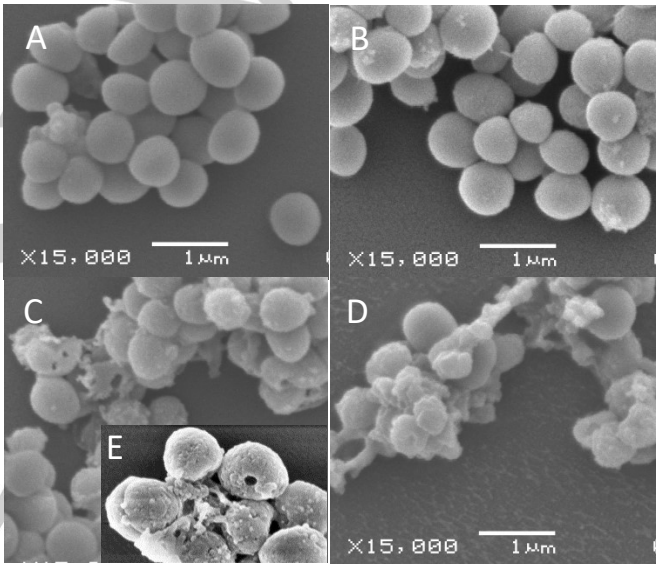


Figure 3. SEM micrographs of *S. Aureus* cells A) Cultures in log phase at 10^8 CFU/ml at T = 0; B) untreated after 18h; C) treated with the dodecamer **7** at the MIC (6.3 μM) after 18h; D) treated with the hexamer **3** at the MIC (3.1 μM) after 18h; E) Field emission gun SEM of *S. Aureus* cells treated with the dodecamer **7** at the MIC (6.3 μM) after 18h.

In the control samples (untreated *S. aureus*), the cells appeared with round and smooth surfaces in grape-like clusters (Figure 3A,B). Upon treatment with the peptoid **7** at the MIC, cytoplasmic leakage and membrane damage were observed (Figure 3C,E). Cells showed surface depressions and some of them had holes (≈ 70-80 nm diameter) in their cell wall. Pore formation has been previously observed on MRSA membrane treated with cyclic peptoids.[12b] SEM micrographs of bacteria treated with the hexamer **3** at the MIC showed significant morphological alterations such as membrane corrugation, but no pores have been detected (Figure 3 D).

In this study, three series of 1,2,3-triazolium-based cationic amphipathic peptoid oligomers have been efficiently synthesized on support. Among them, nonamers **9** and **10** showed potent activities (MIC ≤ 3 μM) especially against *E. faecalis* and *S.*

aureus strains, and good selectivity. Besides, the short hexamer **3** was also active against Gram-positive bacteria and absolutely non-haemolytic and non-cytotoxic on Hela cells. SEM visualization of *S. aureus* cells treated with peptoids **3** or **7** revealed severe cell membrane damages. Our observations suggest that the longest peptoid **7** acts by pore formation while the hexamer **3** seems to cause membrane permeation by another mechanism. This work highlights the potential of triazolium-based cationic amphipathic peptoids for the development of selective antimicrobial agents. Further studies will be conducted to improve their potency and to better understand their mechanism of action.

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Keywords: antimicrobial peptides • peptidomimetics • foldamers • peptoids •solid-phase synthesis

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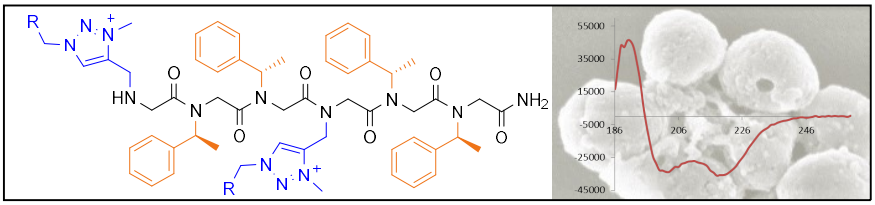

Triazolium as cationic pendant group and helix inducer: Rapidly and efficiently synthesized on solid-phase, amphipathic helicalpeptoid oligomers incorporating 1,2,3-triazolium-type side chain as a cationic moiety and structuring element, were evaluated against *Escherichia coli, Enterococcus faecalis* and *Staphylococcus aureus.* These amphipathic oligomers, even of short length, selectively kill bacteria over mammalian cells.