



HAL
open science

Design of Triazolium-Grafted Peptidomimetic Macrocycles with Facial Amphipathicity to Target Pathogenic Bacteria

Cassandra Guerinot, Mélodie Malige, Nicolas Charbonnel, Killian Malosse,
Laurent Jouffret, Claude Taillefumier, Olivier Roy, Christiane Forestier,
Sophie Faure

► **To cite this version:**

Cassandra Guerinot, Mélodie Malige, Nicolas Charbonnel, Killian Malosse, Laurent Jouffret, et al..
Design of Triazolium-Grafted Peptidomimetic Macrocycles with Facial Amphipathicity to Target
Pathogenic Bacteria. *Organic Letters*, 2024, 26 (19), pp.4088-4092. 10.1021/acs.orglett.4c01149 .
hal-04749521

HAL Id: hal-04749521

<https://uca.hal.science/hal-04749521v1>

Submitted on 23 Oct 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Design of triazolium-grafted peptidomimetic macrocycles with facial amphipathicity to target pathogenic bacteria.

Cassandra Guerinot,¹ Mélodie Malige,² Nicolas Charbonnel,² Killian Malosse,¹ Laurent Jouffret,¹ Claude Taillefumier,¹ Olivier Roy,¹ Christiane Forestier,² Sophie Faure^{1,*}

1. *Université Clermont Auvergne, Clermont Auvergne INP, CNRS, ICCF, F-63000 Clermont–Ferrand, France; [0000-0001-5033-9481](https://orcid.org/0000-0001-5033-9481); Sophie.Faure@uca.fr*
2. *Université Clermont Auvergne, CNRS, LMGE, F-63000 Clermont–Ferrand, France.*

Nature through evolution optimizes native substances to mature bioactive scaffolds with optimal properties. A major maturation process is macrocyclization which explains why many macrocycles are produced by living organisms.^{1,2} These include a number of macrocyclic peptides and depsipeptides such as Gramicidin S, Tyrocidins, Polymyxins and Protegrin I which have led to the discovery of clinical-stage antibiotics or marketed drugs.³ For example, Tyrocidines and Gramicidin S are membrane-active cationic cyclodecapeptides adopting constrained β -hairpin structures with different level of amphipathicity.⁴ These broad-spectrum cyclopeptides possess a multifaceted mode of action which could explain the absence of bacterial resistance after decades of use for skin infections.⁵ Although antimicrobial natural β -hairpin macrocycles usually are not always free of drawbacks in terms of selectivity and biodisponibility, they represent a great source of inspiration for the *de novo* design of potent and selective cyclic peptides/pseudopeptides incorporating unnatural amino acids or amino acid mimics.^{6,4b} In the domain of *N*-alkylglycine peptidomimetics, *i.e.* peptoids,⁷ the potential of macrocycles featuring ammonium type side chains has been explored.⁸ The positive impact of cyclisation on antimicrobial activity and membrane permeation has been demonstrated.^{8b,9} By far less studied than linear peptoid oligomers,¹⁰ cyclopeptoids thus appear to be promising antimicrobial agents that deserve special attention.¹¹ Interested by antimicrobial foldamers,¹² we have recently reported triazolium-based linear peptoids with an amphipathic PolyProline I-type helical structure.¹³ We showed that the use of 1,2,3-triazolium instead of ammonium as cationic groups was decisive for maintaining the activity of short oligomers. We thus envisioned that triazolium-grafted macrocycles might have great potential as antimicrobials. To our knowledge, sequence-defined peptidic/peptidomimetic macrocycles featuring several triazolium pendant groups have never been reported. Indeed, triazolium grafting has been mainly exploited in the polymer field and previously reported macrocycles contain the triazolium moieties on their backbone.¹⁴ Here, we report on the synthesis and study of cyclopeptoids featuring 1,2,3-triazolium-type side chains designed to exhibit facial amphipathicity (Figure 1). We have chosen to retain the same design principles as previously reported antimicrobial cyclopeptoids to highlight the added value of the triazolium-based side chains.⁸ Therefore, an alternation of cationic and hydrophobic side chains was employed according to the generic structure presented (Figure 1).

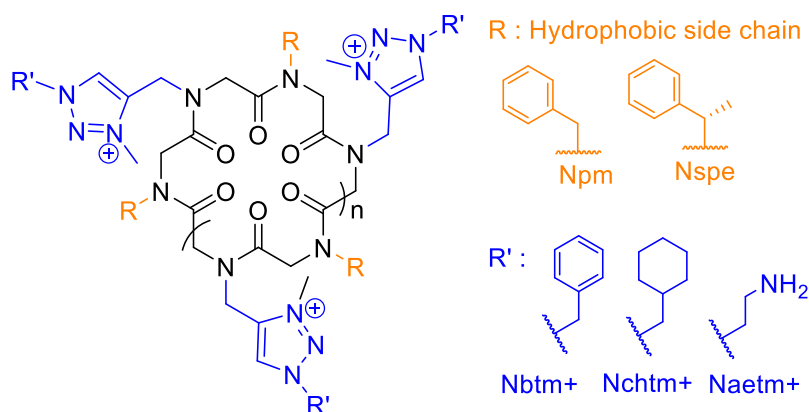
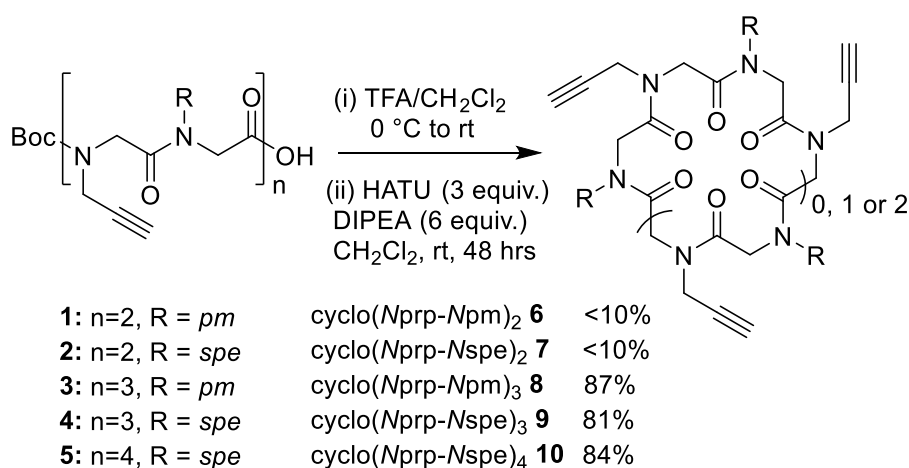


Figure 1. Generic structure of the studied cyclic peptoids.[‡]

The variation of the substituent in position 3 of the triazoliums allowed us to enhance hydrophobic (R' =benzyl), lipophilic (R' =cyclohexyl) or cationic (R' =aminoethyl) character of the entire structure and thus explored the influence on antimicrobial activity. The best strategy to access a panel of macrocycles carrying diversely substituted triazoliums, was to post-modify macrocycles bearing propargyl groups as precursors to triazolium-based side chains. Linear peptoid precursors were synthesized by solid-phase synthesis on 2-chlorotrityl chloride resin by applying the submonomer method and using benzylamine (pm), (*S*)-phenylethyl (spe) and propargylamine (prp) as primary amines.⁷ Two tetramers (**1-2**), two hexamers (**3-4**) and an octamer (**5**) were obtained in yields ranging from 45 to 62% (Scheme 1, ESI). Head-to-tail cyclization efficiency was evaluated using a panel of coupling reagents: the carbodiimide EDCI in presence of HOBT,¹⁵ the phosphonium PyBOP,^{8b,16} the uronium agents HATU¹⁶ and COMU,¹⁷ and the Mukaiyama reagent.¹⁸ This preliminary study quickly went in favor of HATU since other coupling reagents led to macrocycles with yields not exceeding 10%. An additional level of optimization was carried out with HATU/DIPEA, varying the number of equivalents, solvent (DCM or DMF) and concentration (Scheme 1). After work-up and minimal purification by trituration in ether, the two cyclohexamers **8-9** and cyclooctamer **10** were obtained in excellent yields ranging from 81 to 87%. Unfortunately, tetramers **1** and **2** did not lead to cyclotetramers. According LC-MS spectra, cyclooctamer appear to be the predominant macrocycle formed even when using a high dilution protocol developed to circumvent cyclodimerisation issues.¹⁹

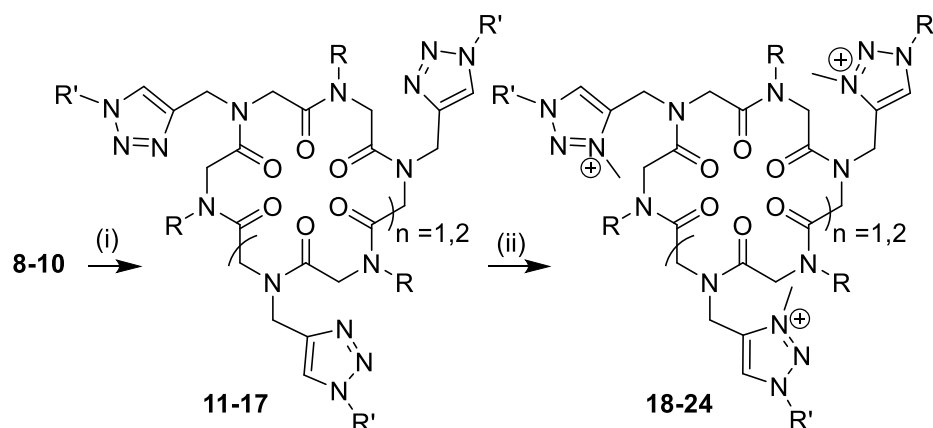
Scheme 1. Head-to-tail cyclization of linear peptoids **1-5**



The three macrocycles were then subjected to multivalent post-modifications to create the cationic side chains (Table 1). Two steps were necessary to obtain triazolium groups from the propargyl side chains.²⁰ Firstly, a Copper-catalyzed Azide-Alkyne cycloaddition (CuAAC) using copper (II) sulfate and ascorbic acid as reducing agent in a water/*tert*-butanol media provided 1,2,3-triazoles with various

substituents. The second step involved quaternization using iodomethane to furnish 1,3-substituted 1,2,3-triazoliums. Overall, this multiple post-modification process proved not trivial due to incomplete conversions leading to partially modified macrocycles. However, after adjustment of the experimental conditions, 14 modified macrocycles comprising triazole side chains (cycles **11-17**) or triazolium side chains (cycles **18-24**) were obtained (Table 1).

Table 1. Access to triazole-/triazolium-grafted macrocycles



Cpd	Modified macrocycles	Yield (%) ^a	Purity (%) ^b
11	cyclo(Nbtm-Npm) ₃	54	91
12	cyclo(Nbtm-Nspe) ₃	91	86
13	cyclo(Nchtm-Nspe) ₃	34	95
14	cyclo(Naetm-Nspe) ₃	66	88
15	cyclo(Nbtm-Nspe) ₄	73	- ^c
16	cyclo(Nchtm-Nspe) ₄	29	- ^c
17	cyclo(Naetm(Boc)-Nspe) ₄	52	- ^c
18	cyclo(Nbtm ⁺ -Npm) ₃	54	94
19	cyclo(Nbtm ⁺ -Nspe) ₃	67	- ^c
20	cyclo(Nchtm ⁺ -Nspe) ₃	48	- ^c
21	cyclo(Naetm ⁺ -Nspe) ₃	57	88
22	cyclo(Nbtm ⁺ -Nspe) ₄	24	- ^c
23	cyclo(Nchtm ⁺ -Nspe) ₄	48	- ^c
24	cyclo(Naetm ⁺ -Nspe) ₄	88	- ^c

Key conditions: (i) $R'N_3$ (3 equiv. per propargyl), aq. $CuSO_4$ (0.48 equiv.; 0.1 M), ascorbic acid (1.44 equiv.; 0.1 M), t -BuOH (0.1 M), rt; (ii) CH_3I (60 equiv.), CH_3CN , $70^\circ C$. ^aIsolated yield; ^bHPLC purity (214 nm); ^cPurity validated by LC-MS/HRMS.

In order to compare the activity of linear and cyclic compounds, a series of linear oligomers with the same sequences were prepared. A free terminal amine and a primary amide at C-terminus were chosen to correlate activities with those of PPI-type peptoids reported in the literature. Using a straightforward solid-phase approach,¹³ triazolium- or triazole-grafted hexapeptoids **25-28** and octapeptoids **29-31** were efficiently obtained in 17 and 21 steps, respectively (Table 2).

Table 2. Triazolyl-/triazolium-grafted linear oligomers

Cpd	Sequence	Yield (%) ^a	Purity (%) ^b
25	H-(Nbtm ⁺ -Nspe) ₃ -NH ₂	76	95
26	H-(Nchtm ⁺ -Nspe) ₃ -NH ₂	75	97
27	H-(Naetm-Nspe) ₃ -NH ₂	37	86
28	H-(Naetm ⁺ -Nspe) ₃ -NH ₂	75	91
29	H-(Nbtm ⁺ -Nspe) ₄ -NH ₂	84	96
30	H-(Nchtm ⁺ -Nspe) ₄ -NH ₂	81	98
31	H-(Naetm ⁺ -Nspe) ₄ -NH ₂	89	97

^aYield after trituration in ether or pentane; ^bHPLC (214 nm).

It is well established that the antibacterial activity of cationic peptides/peptidomimetics is highly dependent on their capacity to adopt an amphipathic architecture when interacting with the negatively charged bacterial membrane.⁵ It was therefore important to study the conformational preferences of these macrocycles to scrutinize their propensity to exhibit amphipathic character.

First, in the hexamer series, crystallization of macrocycle *cyclo*(Nprp-Nspe)₃ **9** in methanol-*d*₄, led to monocrystals suitable for X-ray diffraction. The 18-membered ring **9** belongs to the P21/c space group and adopts a hairpin shape with a *cis-cis-trans-cis-cis-trans* (*cctcct*) arrangement of the backbone amides (Figure 2). This arrangement results in the segregation of the propargyls, precursor of the cationic groups, on the same face of the macrocycle, the hydrophobic groups occupying the other face. This solid-state conformation is the most commonly observed for cyclohexapeptoids.^{19,21} In solution, the ¹H NMR spectra of macrocycle **9** in various solvents (CD₃OD, CD₃CN and CDCl₃) revealed the coexistence of two sets of signals corresponding to two conformations in an approx. 70:30 ratio. The conformation of the amide bonds bearing the *spe* side chain was determined by examining the benzylic chemical shifts, around 6 ppm for a *cis* conformation and 5 ppm for a *trans* conformation.²² We observed that the major conformer comprised two *cis* and one *trans* α -methyl benzyl amides corresponding to the *cctcct* conformation of the crystal structure (Figure 2). The minor conformer showed one *cis* and two *trans* α -methyl benzyl amides which could be attributed to a *ttcttc* arrangement. This arrangement also leads to a up and down positioning of the side chains but has so far only been observed in one single crystal structure,²³ cyclohexapeptoids generally adopting the *cctcct* or *tttttt* arrangements.²⁴ The solid-state structure of post-modified macrocycles could not be obtained. However, ¹H NMR spectra of triazole- and triazolium-grafted cyclohexamers *cyclo*(Nxx-Nspe)₃ suggested a preferred conformation similar to that of the precursor **9**, according to the benzylic chemical shifts and the proton signals from triazolium groups (ESI, Figure S7 for a comparison of macrocycles **9**, **12** and **19**). By contrast, the linear oligomers showed no preferential conformation in solution as indicated by coalescence phenomena and the large number of triazolium proton signals (ESI Figure S9).

In the octamer series, we were not able to obtain monocrystals for X-ray diffraction. Nonetheless, the macrocycle **10** was found to adopt a predominant conformation in solution. Indeed, the ¹H NMR spectrum in different solvents (CD₃OD, CD₃CN, CDCl₃) showed a major set of well-resolved signals (>90% in CDCl₃) whose number is halved relative to the total number of protons, indicating a second-order symmetry (Figure 3 and ESI, Figure S10). A variable-temperature NMR study revealed strong coalescence at temperature above 358K in DMSO-*d*₆ indicating good stability of the preferred conformation until 348K (ESI, Figure S11). 2D NMR experiments were performed to allow proton assignment and determination of the amide conformations (Figure 3, ESI). A *ccttcctt* arrangement was found which corresponds to the main conformation previously identified in cyclooctapeptoid crystal structures.²³

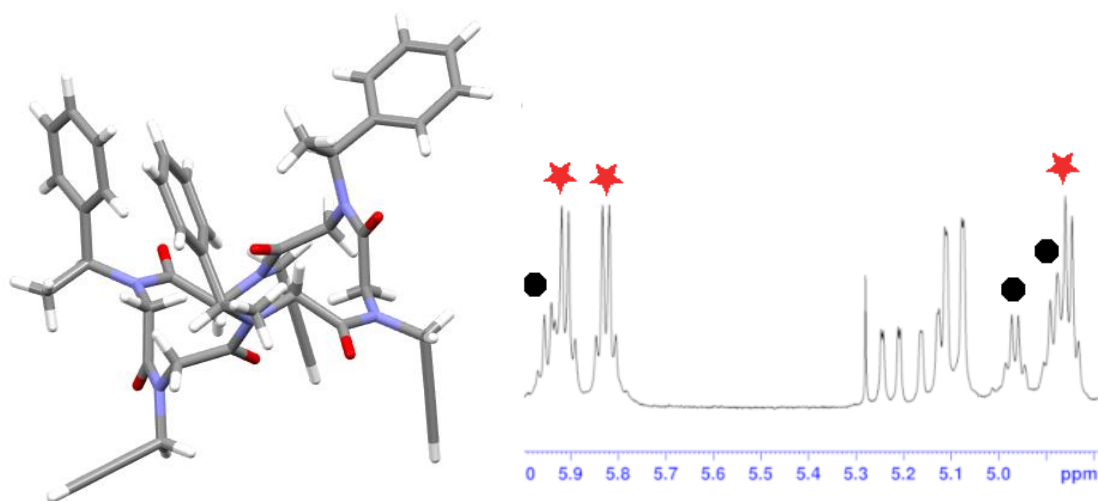


Figure 2. X-ray crystal structure (left) and benzylic proton shift region of the ^1H NMR spectrum (CDCl_3 , 8 mM, 278K) (right) of macrocycle **9**.

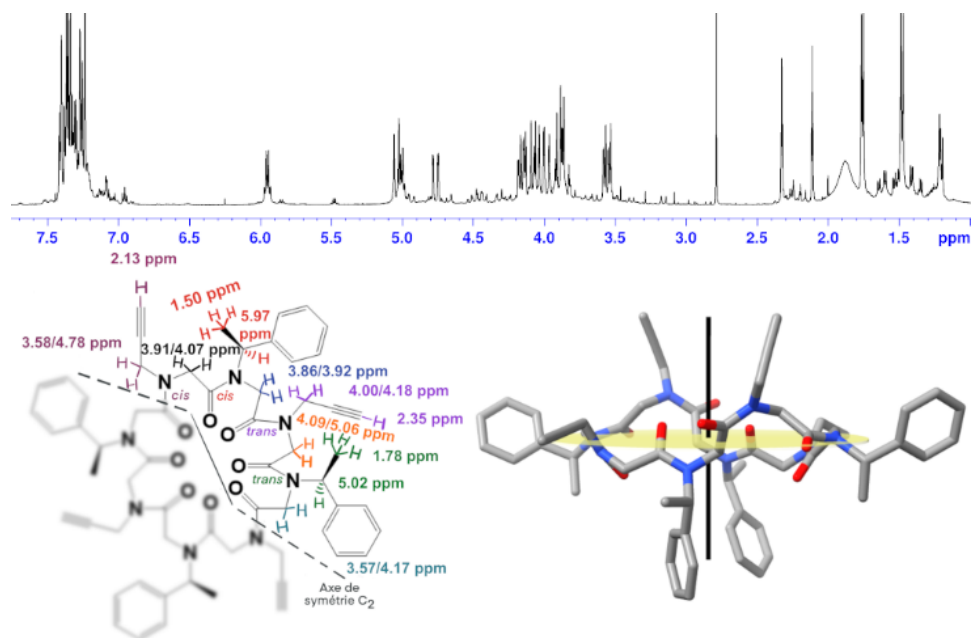


Figure 3. ^1H NMR spectrum (CDCl_3 , 8 mM, 278K) of cyclooctamer **10**, structure with proton assignment and 3D-structure.

According to a model that we built from a reported X-ray structure,²³ then minimized using Gaussian B3LYP 6-31G (d,p), the macrocycle adopts a slightly twisted hairpin structure with an alternated distribution of the side chains on either side of the mean plane. This arrangement is therefore favorable to obtaining the amphipathic character. Examination of the NMR spectra of the modified cyclooctamers **15-24** revealed the presence of more than one defined conformation in solution, particularly for macrocycles **23** and **24**, indicating that the triazole/triazolium side chains have an impact on conformational preferences in the octamer series. This is probably due to significant backbone to side chain $n \rightarrow \pi^*_{Ar}$ electronic interactions^{22b} in these larger and thus less constrained macrocycles. Nevertheless, the spectra of linear octamers still revealed much higher conformational heterogeneity on the NMR time scale than their cyclic counterparts (ESI, Figure S16). This NMR study suggested that the hairpin structure with facial amphipathicity is a preferred conformation in the cyclohexamer series but that the amphipathic character might be less pronounced in the cyclooctamer series.

To evaluate the potential of these triazolyl/triazolium-grafted macrocycles *versus* linear oligomers with the same design, the antimicrobial activity against both Gram-negative and Gram-positive bacteria was determined for ten cyclic and seven linear peptoids (Table 3).

Table 3. Antibacterial activities (MIC/MBC)^a of cyclic and linear triazole/triazolium-grafted peptoids

Cpd	charge	<i>E. coli</i>	<i>P.aeruginosa</i>	<i>S. aureus</i>
	12	0	>100/>100	>100/>100
C	13	0	>100/>100	>100/>100
Y	14	+3	>100/>100	>100/>100
C	18	+3	>100/>100	>100/>100
L	19	+3	>100/>100	50/>100
I	20	+3	25/>100	3,2/50
C	21	+6	>100/>100	>100/>100
	22	+4	12,5/50	3,2/3,2
	23	+4	50/100	12.5/12.5
	24	+8	>100/>100	>100/>100
	25	+3	100/>100	12,5/100
L	26	+3	25/100	3,2/50
I	27	+3	>100/>100	>100/>100
N	28	+6	>100/>100	>100/>100
E	29	+4	25/50	6,25/6,25
A	30	+4	6,25/25	1,6/12,5
R	31	+8	>100/>100	>100/>100

^aMinimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) (μ M) were determined on *E. coli* ATCC25922, *P. aeruginosa* ATCC27853 and *S. aureus* CIP6525 using the standard micro broth dilution method. Data are representative of three independent experiments.

This screening first showed that cyclic or linear hexamer with uncharged triazolyl side-chains (**12-14** and **27**) were all inactive, even in the presence of ammonium groups (**14** and **27**). In the cyclohexamer series, only the macrocycle cyclo(*N*chtm⁺-*Nspe*)₃ **20** exhibited activities, particularly on *S. aureus*. However, it appears to be a bacteriostatic effect rather than a bactericidal effect according to MBC. Its linear counterpart **26** showed very similar activities indicating that cyclisation is not, in this case, a determining factor. Indeed, it appears that the activities are strongly dependent on the nature of the substituent on the triazolium groups (MIC for (*N*chtm⁺-*Nspe*)₃<(*N*btm⁺-*Nspe*)₃<(aetm⁺-*Nspe*)₃). By increasing sequence size up to the octamer, better activities on *E. coli* and *S. aureus* strains were generally observed (cyclohexamer **19** versus cyclooctamer **22** and linear hexamer **26** versus linear octamer **30**). However, octapeptoids with additional positive charges due to the presence of ammonium groups (*Naetm*⁺) were still inactive, indicating that the best balance between cationic and hydrophobic groups was in favor of hydrophobicity as previously observed.^{8c} None of these cationic amphipathic peptoids had any effect on *P. aeruginosa*. Finally, the toxicity of the five most potent peptoids was evaluated (Figure 4). The results revealed that in the hexamer series, the toxicity profiles of cyclo(*N*chtm⁺-*Nspe*)₃ **20** and its linear equivalent **26** are very similar, but in the octamer series, H-(*N*btm⁺-*Nspe*)₄-NH₂ **29** proves to be really less toxic than its cyclic equivalent **22**. This result suggests that a more constrained structure is detrimental to the selectivity profile of these triazolium-grafted peptoids. However, the nature of the side chains also has a strong influence, as illustrated by the toxicity of H-(*N*chtm⁺-*Nspe*)₄-NH₂ **30** compared to that of H-(*N*btm⁺-*Nspe*)₄-NH₂ **29**. This study clearly shows that this class of triazolium-grafted peptoids, even short ones, has interesting activities on *S. aureus*

but, unlike other classes of antimicrobial peptoids, no benefit in terms of activity or selectivity is gained by cyclization.

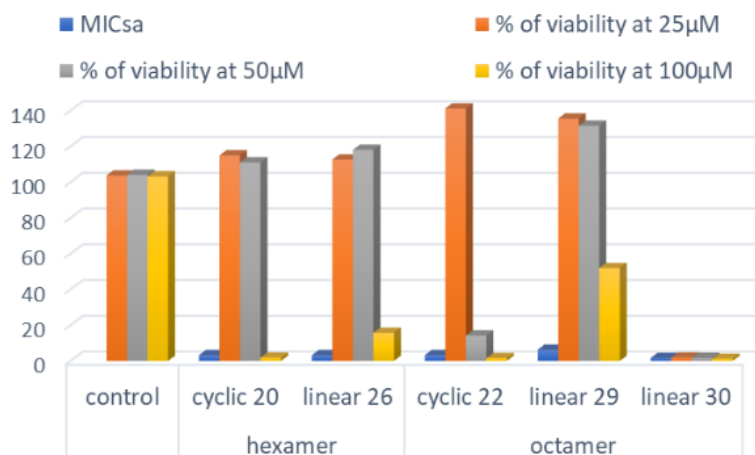


Figure 4. Comparison of the MIC for *S. aureus* and the percentage of viable HeLa cells after 24h exposition (MTT assay).

In conclusion, triazolium-grafted peptoid oligomers have been prepared on solid-phase for linear series and in solution from the cyclisation step to access the cyclic series. The strategy has enabled the introduction of diverse triazolium-type side chains by a two-step multivalent post-modification. Conformational analysis of cyclohexamer **9** and cyclooctamer **10** has shown that both adopt a preferred hairpin structure with an alternated distribution of side chains on either side of the mean plane of the macrocycle, necessary to achieve facial amphipathic character of the designed triazolium-grafted macrocycles. A preliminary study has revealed interesting antibacterial activities that strongly depend on the positioning and nature of the triazolium side chains rather than on the cyclic or linear nature of the oligomer.

ACKNOWLEDGMENT

This work was supported by the project ANR-20-CE18-0021-01. CG acknowledges ANR for PhD grant.

REFERENCES

- ‡ Peptoid residues nomenclature: *Npm* for *N*-(phenylmethyl)glycine, *Nspe* for (S)-*N*-(1-phenylethyl)glycine, *Nbtm*⁺ for *N*-(1-benzyl-3-methyl-1,2,3-triazolylmethyl)glycine, *Nchtm*⁺ for *N*-(1-cyclohexylmethyl-3-methyl-1,2,3-triazolylmethyl)glycine, *Naetm*⁺ for *N*-(1-(2-aminoethyl)-3-methyl-1,2,3-triazolylmethyl)glycine.
- (1) Hamley, I. W. Small Bioactive Peptides for Biomaterials Design and Therapeutics, *Chemical Reviews* **2017**, *117*, 14015-14041.
 - (2) Walsh, C. T. Nature Builds Macrocycles and Heterocycles into Its Antimicrobial Frameworks: Deciphering Biosynthetic Strategy. *ACS Infectious Diseases* **2018**, *4*, 1283-1299.
 - (3) Luther, A.; Bisang, C.; Obrecht, D. Advances in macrocyclic peptide-based antibiotics. *Bioorg. Med. Chem.* **2018**, *26*, 2850–2858.
 - (4) (a) Munyuki, G.; Jackson, G. E.; Venter, G. A.; Kövér, K. E.; Szilágyi, L.; Rautenbach, M.; Spatself, B. M.; Bhattacharya, B.; van der Spoel, D. β -Sheet Structures and Dimer Models of the Two Major Tyrocidines, Antimicrobial Peptides from *Bacillus aneurinolyticus*. *Biochemistry* **2013**, *52*, 7798-7806 (b) Lee, D.L.; Hodges, R.S. Structure–activity relationships of de novo designed cyclic antimicrobial peptides based on gramicidin S. *Biopolymers* **2003**, *71*, 28-48.
 - (5) Wenzel, M.; Rautenbach, M.; Vosloo, J.A.; Siersma, T.; Aisenbrey, C.H.M.; Zaitseva, E.; Laubscher, W.E.; van Rensburg, W.; Behrends, J.C.; Bechinger, B.; Hamoen, L.W. The Multifaceted Antibacterial Mechanisms of the Pioneering Peptide Antibiotics Tyrocidine and Gramicidin S. *mBio* **2018**, 9:e00802-18.
 - (6) (a) Laurencin, M.; Amor, M.; Fleury, Y.; Baudy-Floc'h M. De Novo Cyclic Pseudopeptides Containing Aza- β -amino Acids Exhibiting Antimicrobial Activities. *J. Med. Chem.* **2012**, *55*, 10885-10895. (b) Hu, C.; Wen, Q.; Huang, S.; Xie, S.; Fang, Y.; Jin, Y.; Campagne, R.; Alezra, V.; Miclet, E.; Zhu, J.; Wan, Y. Gramicidin-S-Inspired Cyclopeptidomimetics as Potent Membrane-Active Bactericidal Agents with Therapeutic Potential.

- ChemMedChem* **2021**, *16*, 368–376. (c) Robinson, J. A. β -Hairpin Peptidomimetics: Design, Structures and Biological Activities. *Acc. Chem. Res.* **2008**, *41*, 1278–1288.
- (7) Zuckermann, R. N.; Kerr, J. M.; Kent, S. B. H.; Moos, W. H. Efficient method for the preparation of peptoids by submonomer solid-phase synthesis. *J. Am. Chem. Soc.* **1992**, *114*, 10646–10647.
- (8) (a) Comegna, D.; Benincasa, M.; Gennaro, R.; Izzo, I.; De Riccardis, F. Design, synthesis and antimicrobial properties of non-hemolytic cationic β -cyclopeptoids. *Bioorg. Med. Chem.* **2010**, *18*, 2010–2018. (b) Huang, M. L.; Shin, S. B. Y.; Benson, M. A.; Torres, V. J.; Kirshenbaum, K. A Comparison of Linear and Cyclic Peptoid Oligomers as Potent Antimicrobial Agents. *ChemMedChem* **2012**, *7*, 114–122. (c) Huang, M. L.; Benson, M. A.; Shin, S. B. Y.; Torres, V. J.; Kirshenbaum, K. Amphiphilic cyclic peptoids that exhibit antimicrobial activity by disrupting *Staphylococcus aureus* membranes. *Eur. J. Org. Chem.* **2013**, *17*, 3560–3566.
- (9) Andreev, K.; Martynowycz, M.W.; Ivankin, A.; Huang, M.L.; Kuzmenko, I.; Meron, M.; Lin, B.; Kirshenbaum, K.; Gidalevitz, D. Cyclization Improves Membrane Permeation by Antimicrobial Peptoids. *Langmuir* **2016**, *32*, 12905–12913.
- (10)(a) Patch, J.A.; Barron A.E. Helical Peptoid Mimics of Magainin-2 Amide. *J. Am. Chem. Soc.* **2003**, *125*, 12092–12093. (b) Mojsoska, B.; Zuckermann, R.N.; Jenssen, H. Structure-Activity Relationship Study of Novel Peptoids That Mimic the Structure of Antimicrobial Peptides. *Antimicrob. Agents Chemother.* **2015**, *59*, 4112–4120. (c) Bicker, K. L.; Cobb, S. L. Recent advances in the development of anti-infective peptoids. *Chem. Commun.* **2020**, *56*, 11158–11168.
- (11) D’Amato, A. Structure – Bioactivity Relationship in Cyclic Peptoids: An Overview. *Eur. J. Org. Chem.* **2022**, *38*, e202200665.
- (12) Yokoo, H.; Hirano, M.; Misawa, T.; Demizu, Y. Helical Antimicrobial Peptide Foldamers Containing Non-proteinogenic Amino Acids. *ChemMedChem* **2021**, *16*, 1226–1233.
- (13) Shyam, R.; Charbonnel, N.; Job, A.; Blavignac, C.; Forestier, C.; Taillefumier, C.; Faure, S. 1,2,3-Triazolium-Based Cationic Amphipathic Peptoid Oligomers Mimicking Antimicrobial Helical Peptides. *Chem. Med. Chem.* **2018**, *13*, 1513–1516.
- (14) (a) Song, J.; Lv, J.; Jin, J.; Jin, Z.; Li, T.; Wu, J. Research Advances on the Bioactivity of 1,2,3-Triazolium Salts. *Int. J. Mol. Sci.* **2023**, *24*, 10694. (b) Safarnejad Shad, M.; Santhini, P.V.; Dehaen, W. 1,2,3-Triazolium macrocycles in supramolecular chemistry. *Beilstein J. Org. Chem.* **2019**, *15*, 2142–2155.
- (15) Caumes, C.; Fernandes, C.; Roy, O.; Hjelmgaard, T.; Wenger, E.; Didierjean, C.; Taillefumier, C.; Faure, S. Cyclic α,β -tetrapeptoids: sequence-dependent cyclization and conformational preference. *Org. Lett.* **2013**, *15*, 3626–3629.
- (16) Webster, A. M.; Cobb, S. L. Recent Advances in the Synthesis of Peptoid Macrocycles. *Chem. Eur. J.* **2018**, *24*, 7531–7780.
- (17) Hjelmgaard, T.; Nauton, L.; De Riccardis, F.; Jouffret, L.; Faure, S. Topologically Diverse Shapes Accessible by Modular Design of Arylopeptoid Macrocycles. *Org. Lett.* **2018**, *20*, 268–271.
- (18) Pollastrini, M.; Pasquinelli, L.; Górecki, M.; Balzano, F.; Cupellini, L.; Lipparini, F.; Uccello Barretta, G.; Marchetti, F. Pescitelli, G.; Angelici, G. A Unique and Stable Polyproline I Helix Sorted out from Conformational Equilibrium by Solvent Polarity. *J. Org. Chem.* **2022**, *87*, 13715–13725.
- (19) D’Amato, A.; Pierri, G.; Tedesco, C.; Della Sala, G.; Izzo, I.; Costabile, C.; De Riccardis, F. Reverse Turn and Loop Secondary Structures in Stereodefined Cyclic Peptoid Scaffolds. *J. Org. Chem.* **2019**, *84*, 10911–10928.
- (20) Aliouat, H.; Caumes, C.; Roy, O.; Zoukri, M.; Taillefumier, C.; Faure, S. 1,2,3-Triazolium-Based Peptoid Oligomers. *J. Org. Chem.* **2017**, *82*, 2386–2398.
- (21) (a) Yoo, B.; Shin, S. B. Y.; Huang M. L.; Kirshenbaum, K. Peptoid Macrocycles: Making the Rounds with Peptidomimetic Oligomers. *Chem. Eur. J.* **2010**, *16*, 5528–5537. (b) De Riccardis, F. The Challenge of Conformational Isomerism in Cyclic Peptoids. *Eur. J. Org. Chem.* **2020**, *20*, 2981–2994 and references cited therein.
- (22) (a) Kirshenbaum, K.; Barron, A. E.; Goldsmith, R. A.; Armand, P.; Bradley, E. K.; Truong, K. T. V.; Dill, K. A.; Cohen, F. E.; Zuckermann, R. N. Sequence-specific polypeptoids: A diverse family of heteropolymers with stable secondary structure. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 4303 – 4308. (b) Caumes, C.; Roy, O.; Faure, S.; Taillefumier, C. The click triazolium peptoid side chain: a strong cis-amide inducer enabling chemical diversity. *J. Am. Chem. Soc.* **2012**, *134*, 9553–9556.
- (23) Jiang, L.; Hu, C. T.; De Riccardis, F.; Kirshenbaum K. Elaborate Supramolecular Architectures Formed by Co-Assembly of Metal Species and Peptoid Macrocycles. *Cryst. Growth Des.* **2021**, *21*, 3889–3901.
- (24) Eastwood, J. R. B.; Jiang, L.; Bonneau, R.; Kirshenbaum, K.; Renfrew, P. D. Evaluating the Conformations and Dynamics of Peptoid Macrocycles. *J. Phys. Chem. B* **2022**, *126*, 5161–5174 and references cited therein