Ideal Chemical and Structural Properties of Peptoid Antimicrobials

Lucas Sheppard, Dr. Thu Nguyen
Lake Superior State University
School of Science & Medicine

Introduction

- Antibiotic resistance is a growing, global threat to humanity[1]
- Many actions, including discovery of new antibiotics, are necessary to combat it[1]
- Peptoids represent new antibiotics which are structurally similar to peptides[2]
- Peptoids display many properties which make them more effective than peptides such as proteolysis resistance[3]

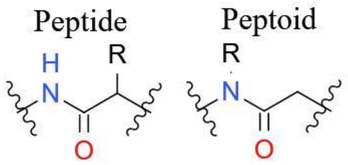

Figure 1. Structures of peptoid and peptide monomers.

- This review discusses the structural and chemical properties which lend to a peptoid's efficacy and what properties can be optimized to make a peptoid ideal

Methods

- Search terms: "peptoids," "peptoid antibiotics," "peptoids v peptides," "peptoid mechanisms," and related terms in Google Scholar
- Papers used to determine degree of antibacterial efficacy and cytotoxic properties
- Antimicrobial activity and structures used to determine necessary features of peptoids
- Data processed to find broad average activity ratings for each agent against gram positive and gram negative bacteria
- Peptoid structure-activity reports found in literature from previous search and specific serach
- Structure-activity reports used to solidify information on important peptoid properties

Peptoids vs Pathogens

- Many peptoids display broad spectrum efficacy, but best MICs are against gram-positive bacteria[4]

Table 1. MIC values of Peptoid 1 and C_{13}-1_{4mer} against various microbes of different classes. Gram-stain labeled with +(positive) or –(negative).[5]

Peptoid	MIC (μg/ml) for:			
	E. Coli(+)	B. Subtilis(-)	C. albicans	M. tuberculosis
1	14.7	3.7	14.7	14.1
C_{13}-1_{4mer}	14	1.8	14	6.6

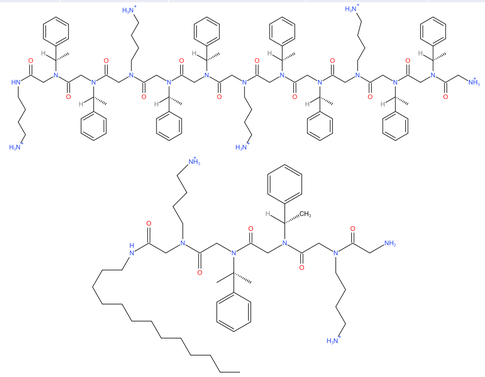

Figure 3. 2-D structures of Peptoid 1(above) and C13-1_{4mer}(below).

- Peptoids show efficacy against tough bacteria such as *M. tuberculosis*

Table 2. MIC values (μM) for various peptoids versus drug resistant bacteria. (M^r– Methicillin Resistant, Q^r – Quinolone Resistant, VanB – Vancomycin Resistant.)[4]

Peptoid	29498	29496	32133	33091	33092	33670
S. aureus 188 (M^r Q^r)	10	10	10	10	10	5
S. aureus 244 (M^r)	10	10	10	10	10	5
S. epidermidis CNS112 (M^r Q^r)	10	10	10	10	10	5
Enterococcus faecalis 141 (VanB Q^r)	10	5	20	10	20	5

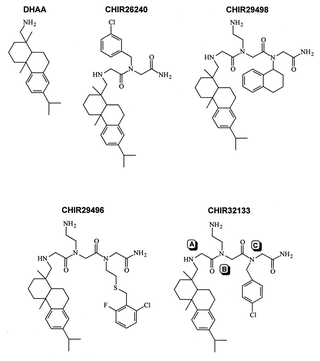

Figure 2.4 Structures of peptoids identified in table 2. The ABC markers adjacent to CHIR32133 symbolize each functional group which. This peptoid was synthesized with multiple sequential isomers as follows: 33090 - ACB; 33091 - BAC; 33092 - BCA; 33670 - CAB; and 33671 – CBA.[4]

- Peptoid 33670 showed the greatest efficacy, with a gram positive average MIC of 6 μM and gram negative average MIC of 16 μM

Chemical Properties

- Chirality did not affect antimicrobial activity, but did affect hemolytic activity
- Lengthened peptoid chains increase cytotoxicity
- Shortening of peptoid 1 below 12 monomers decreased antimicrobial activity
- Anionic and neutral peptoids were ineffective compared to cationic peptoids

Table 3. Structure-activity report of peptoid isomers for multiple properties.[6]

Test	Peptoid	Sequence	E. coli MIC	B. subtilis MIC	SR
Original	1	H-(NLys-[Nspe]$_2$)$_4$-NH_2	3.5	0.88	6
	2	H-(NLys-Nssb-Nspe)$_4$-NH_2	31	3.9	>3.9
Chirality	$1_{enantiomer}$	H-(NLys-Nrpe-Nrpe)$_4$-NH_2	3.5	0.88	4.6
Length	1_{6mer}	H-(NLys-[Nspe]$_2$)$_2$-NH_2	27	27	>8.1
	1_{9mer}	H-(NLys-[Nspe]$_2$)$_3$-NH_2	9.1	1.2	>16
	1_{15mer}	H-(NLys-[Nspe]$_2$)$_5$-NH_2	5.5	1.4	0.55
Hydro-phobicity	2-$Nsmb_{2,5,8,11}$	H-(NLys-Nsmb-Nspe)$_4$-NH_2	7.4	0.95	>16
	2-$Nsna_{6,12}$	H-(NLys-Nssb-Nspe-NLys-Nssb-Nsna)$_2$-NH_2	7.2	0.93	7.6
	1-$Nsna_{6,12}$	H-(NLys-[Nspe]$_2$-NLys-Nspe-Nsna)$_2$-NH_2	3.3	1.6	1.2
	1-$NHis_{6,12}$	H-(NLys-[Nspe]$_2$-NLys-Nspe-NHis)$_2$-NH_2	3.5	6.9	>31
	1-Pro_6	H-NLys-[Nspe]$_2$-NLys-Nspe-l-Pro-(NLys-[Nspe]$_2$)$_2$-NH_2	3.1	1.6	20
Charge +3	1-$NGlu_{4,10}$	H-(NLys-[Nspe]$_2$-NGlu-[Nspe]$_2$)$_2$-NH_2	>110	6.9	<0.2
Charge +5	1-$NGlu_{1,4,7,10}$	H-(NGlu-Nspe-Nspe)$_4$-NH_2	>219	>219	N/A

- Selectivity ratio displays the quotient of *E. coli* MIC and the concentration at which 10% of human red blood cells lysed
- In this display, a high SR means the peptoid is more selective towards bacteria than human cells
- Hydrophobic *Nsmb* and N*sna* residues substituted to test correlation of activity and hydrophobicity
- Substitution with these residues increased antibacterial and hemolytic activities
- Hydrophobicity correlated strongly to cytotoxicity and selectivity ratio as well as antimicrobial efficacy
- Facial 2-D amphipathicity altered activity inconclusively in two reports
- Sequence reordering had definite effect on peptoid activity

Discussion

- Peptoids have more favorable *in vivo* pharmacological properties than analogous peptoids
- Peptoids could be used to permeate membranes for synergistic effect with intracellular targeted antibiotics, this potential should be investigated
- Ideal peptoid properties include: net cationic charge per unit length and low to moderate hydrophobicity
- Each peptoid should be optimized for best selectivity through sequence alteration and shuffling
- Small to medium peptoids are best, too lengthy peptoids are cytotoxic(15 or more residues for peptoid 1)

Conclusions

- Peptoids have displayed efficacy against drug resistant bacteria
- Peptoids have many properties which must be optimized and tested
- Ideal peptoids are of moderate length, cationic, and optimized experimentally for ideal hydrophobicity
- Synergistic effects are deserving of further research

References

1. Antibiotic Resistance Threats in the United States. *Center for Disease Control and Prevention. U.S. Department of Health and Human Services.* **2013**.
2. Zuckermann, R. N.; Kerr J. M.; Kent S. B. H.; Moos W. H.;. *J. Am. Chem. Soc.* **1992**, 114, 10646-10647.
3. Miller, S. M.; Simon, R. J.; Ng, S.; Zuckermann, R. N.; Kerr, J. M.; Moos, W. H.. *Bioorg Med. Chem. Lett.* **1994**, 4, 2657-2662.
4. Goodson, B.; Ehrhardt, A.; Ng.; S; Nuss, J.; Johnson, K.; Giedlin, M.; Yamamoto, R.; Moos, W. H.; Krebber, A.; Ladner, M.; Giacona, M. B.; Vitt, C.; Winter, J. *Antimicrob. Agents Ch.* **1999**, 43, 1429-1434.
5. Kapoor, R.; Eimerman, P. R.; Hardy, J. W.; Cirillo, J. D.; Contag, C.H.; Barron, A. E. *Antimicrob. Agents Ch.* **2011**, 55, 3058-3062.
6. Chongsiriwatana, N. P.; Patch J. A.; Czyzewski, A. M.; Dohm, M. T.; Ivankin, A.; Gidalevitz, D.; Zuckermann, R. N.; Barron, A. E.. *P. Natl. Acad. Sci. USA.* **2008,** 105, 2794-2799.

Acknowledgements

- This research was funded in part by a generous grant from the Lake Superior State University Undergraduate Research Grant