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Short Alkylated Peptoid Mimics of Antimicrobial Lipopeptides[▽]

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We report the creation of alkylated poly-*N*-substituted glycine (peptoid) mimics of antimicrobial lipopeptides with alkyl tails ranging from 5 to 13 carbons. In several cases, alkylation significantly improved the selectivity of the peptoids with no loss in antimicrobial potency. Using this technique, we synthesized an antimicrobial peptoid only 5 monomers in length with selective, broad-spectrum antimicrobial activity as potent as previously reported dodecameric peptoids and the antimicrobial peptide pexiganan.

Antimicrobial peptides (AMPs) (1) are ubiquitously found in nature as an integral component of many organisms' first defense against pathogens (10). Unlike conventional antibiotics, AMPs are largely thought to kill bacteria via nonspecific membrane interactions (5), with a reduced probability that bacteria will develop resistance (11, 14, 28). Several peptidomimetic analogs of AMPs, made of β-peptides (29–32), poly(phenyleneethynylene)s (12, 33), and peptoids (6, 9, 26), have successfully captured AMP-like activity in a nonnatural system.

Peptoids are isomers of peptides where the side chain of each residue stems from the backbone nitrogen instead of the α-carbon (Fig. 1). This change makes peptoids protease resistant (24), thereby increasing their bioavailability. Peptoids with α-chiral side chains can fold into three-sided polyproline type-I-like helices that are ideal for mimicking the amphipathic nature of many AMPs (2, 3, 16, 36, 37). The cost-effective and facile synthesis of peptoids (38), as well as their designable structure and advantageous pharmacological properties, makes peptoids excellent candidates to mimic antimicrobial peptides.

Lipopeptides such as daptomycin and the polymyxin and echinocandin families of clinically approved antibiotics are an increasingly important class of antimicrobial peptides. Polymyxin B (34) and trichogin (27) possess fatty acid moieties that are known to be integral to their activities. In recent years, development of linear antimicrobial peptides has shifted to ever-shorter peptides for synthetic and pharmacological reasons (15, 17, 18, 22, 23), but relatively little work has investigated linear AMPs with hydrophobic tails. Fatty acid tails have been attached to linear antimicrobial peptides that are not normally acylated (4, 19–21), in some cases endowing inactive cationic peptides with antimicrobial activity. Peptoid synthesis enables facile incorporation of an alkylamine into the peptoid as an N-terminal alkyl tail, and thus we use this strategy to investigate alkylated peptoids as mimics of antimicrobial lipopeptides.

Design of peptoids. Previous studies demonstrated the feasibility of peptoid mimicry of AMPs (26), yielding peptoid oligomers 12 to 16 residues in length with low-micromolar, broad-spectrum antibacterial activity and low-to-negligible mammalian cytotoxicity at the bacterial MICs (6, 26). Peptoid 1 [H-(*N*Lys-*N*spe-*N*spe)$_4$-NH$_2$, where *N*Lys is *N*-(4-aminobutyl)glycine and *N*spe is *N*-(*S*)-(1-phenylethyl)glycine] (Table 1) is a dodecameric peptoid with a simple trimer repeat forming an amphipathic helix with one cationic face and two aromatic faces. Using the submonomer approach, we synthesized a series of alkylated analogs of peptoid 1 (38), systematically decreasing the length of the peptoid chain in increments of three monomers (one helical turn), except for the shortest length based on reports of ultrashort AMPs containing two positive charges (15, 17, 22, 23). Alkyl tails were 5, 10, or 13 carbons in length and were incorporated as the side chains of the N-terminal peptoid residue using the appropriate alkylamine for the substitution step. Table 1 lists the names and sequences of the alkylated peptoids investigated (Fig. 1 shows monomer structures).

Antibacterial and antifungal activity. The MICs of the peptoids against bacteria (Gram-negative *Escherichia coli* and Gram-positive *Bacillus subtilis*), determined according to CLSI M07-A6 protocols (7), and *Candida albicans* SC5314, determined according CLSI M27-A2 protocols (25), are shown in Table 1. Data for pexiganan (8), a peptide analog of magainin-2 developed as a topical antimicrobial agent, and melittin, a cytotoxic AMP from bee venom, are included for comparison.

Previous studies have shown peptoid 1 to be potent against both Gram-negative and Gram-positive bacteria, and, with increasing tail length, the more hydrophobic analogues of peptoid 1 retain or start losing their antibacterial activity but increase their antifungal potency. In contrast, alkylated peptoids with base chain lengths of nine, six, and four residues all showed significant improvements in potency against both bacteria and fungi relative to the unalkylated peptoid. The higher

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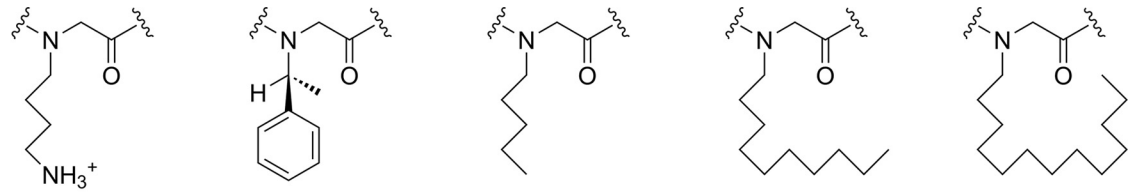

FIG. 1. Peptoid monomer side chain structures, with full and shorthand names.

hydrophobicities required for antifungal activity may result from differences in composition between bacterial (more anionic) and eukaryotic (more zwitterionic) membranes. Therefore, the hydrophobic contribution to fungal membrane adsorption is more important than that to bacterial membrane adsorption. Notably, alkylated peptoids as short as five residues (e.g., *N*tridec-1_{4mer}, where *N*tridec is *N*-tridecylglycine) showed potent antimicrobial activity. We therefore tested the antibacterial activity of peptoid 1 and *N*tridec-1_{4mer} against a broad spectrum of pathogenic bacteria. As shown in Table 2, *N*tridec-1_{4mer} was generally comparable in potency to pexiganan and peptoid 1 against the strains tested.

Hemolytic activity. Lytic activity against human erythrocytes, measured as previously reported (6), was used to gauge mammalian cytotoxicity. Since these compounds are mildly selective for Gram-positive bacteria (Tables 1 and 2), we calculated a selectivity ratio (SR) (Table 1) for each compound as the quotient of the *B. subtilis* MIC and the 10% hemolytic dose (a measure of serious toxicity). Several compounds, such as 1_{9mer}, *N*pent-1_{9mer} (*N*pent, *N*-pentylglycine), *N*dec-1_{6mer} (*N*dec, *N*-decylglycine), *N*dec-1_{4mer}, and *N*tridec-1_{4mer}, exhibited selectivities ranging from 17 to 95, significantly better than the parent peptoid 1 (SR of 8.9). As expected from an increase in hydrophobicity (6), for peptoids with the same number of residues, hemolytic activity increased with the length of the attached alkyl tail, as is readily apparent for the acylated analogs of 1_{9mer} (Table 1). However, alkylation was not always sufficient to cause hemolytic activity, as both *N*pent-1_{6mer} and *N*dec-1_{4mer} exhibited no hemolysis even at concentrations higher than 200 μg/ml.

Short alkylated peptoids may employ modes of killing that are similar to those of nonalkylated, full-length antimicrobial peptoids and peptides (22, 35). In solution, alkylated AMPs may form micelles (22), intertwined peptide-tail structures (13), and nanostructures (23). While ongoing studies in our laboratory are investigating the effect and extent of peptoid oligomerization, micellization may play a role in assembling alkylated peptoids into areas of high local concentration, allowing them to exert their microbicidal effects at lower bulk concentrations relative to unalkylated parent compounds of the same length. Micellization or alternate aggregation methods almost certainly occur, as demonstrated by the great disparity between the low variation in high-performance liquid chromatography (HPLC) elution times (a measurement of hydrophobicity [6]) and the greatly variable calculated log $D_{7.4}$ (log [concentration of the solute in octanol/concentration of the solute in water]) values in Table 1.

The antimicrobial activities of *N*dec-1_{6mer} and *N*tridec-1_{4mer} were comparable to that of peptoid 1, and both demonstrated improved selectivity, with molecular weights 61% and 46% of that of peptoid 1, respectively. Thus, these short peptoid mimics of antimicrobial lipopeptides preserve the potent, broad-

TABLE 1. Antibacterial, antifungal, and hemolytic activities of alkylated ampetoids[a]

Peptoid or peptide	Sequence	MW[b]	% ACN at RP-HPLC elution[c]	Calculated log $D_{7.4}$[d]	MIC (μg/ml) for:			HD_{10}/HD_{50}[e] (μg/ml)	SR[f]
					E. coli	*B. subtilis*	*C. albicans*		
1	H-(*N*Lys-*N*spe-*N*spe)$_4$-NH_2	1,819.3	64.2	−1.11	14.7	3.7	14.7	33/145	8.9
*N*pent-1	H-*N*pent-(*N*Lys-*N*spe-*N*spe)$_4$-NH_2	1,946.5	66.0	1.88	15.5	3.9	15.5	37/128	9.5
*N*dec-1	H-*N*dec-(*N*Lys-*N*spe-*N*spe)$_4$-NH_2	2,016.3	72.5	4.43	31.6	4.0	4.0	13/40	3.3
1_{9mer}	H-(*N*Lys-*N*spe-*N*spe)$_3$-NH_2	1,368.8	60.7	−1.72	45.6	2.9	28.5	274/>365	95
*N*pent-1_{9mer}	H-*N*pent-(*N*Lys-*N*spe-*N*spe)$_3$-NH_2	1,495.9	63.3	1.28	30.8	1.8	23.7	100/>190	56
*N*dec-1_{9mer}	H-*N*dec-(*N*Lys-*N*spe-*N*spe)$_3$-NH_2	1,566.1	70.8	3.83	12.4	6.2	6.2	20/69	3.2
1_{6mer}	H-(*N*Lys-*N*spe-*N*spe)$_2$-NH_2	918.2	47.0	−2.31	>126	>126	>126	>252/>252	ND[g]
*N*pent-1_{6mer}	H-*N*pent-(*N*Lys-*N*spe-*N*spe)$_2$-NH_2	1,045.4	59.4	0.68	>266	4.1	133	>266/>266	>65
*N*dec-1_{6mer}	H-*N*dec-(*N*Lys-*N*spe-*N*spe)$_2$-NH_2	1,115.5	69.8	3.23	8.8	2.2	8.8	37.8/106	17
*N*dec-1_{4mer}	H-*N*dec-(*N*Lys-*N*spe-*N*spe-*N*Lys)-NH_2	793.1	60.1	1.91	>108	6.8	108	>215/>215	>32
*N*tridec-1_{4mer}	H-*N*tridec-(*N*Lys-*N*spe-*N*spe-*N*Lys)-NH_2	835.2	68.0	3.44	14.0	1.8	14.0	73/224	41
Pexiganan	GIGKFLKKAKKFGKAFVKILKK-NH_2	2,477.2	49.2	ND	7.8	3.9	124	181/>495	46
Melittin	GIGAVLKVLTTGLPALISWIKRKRQQ-NH_2	2,846.5	64.3	ND	35.6	4.5	4.5	2.8/17.1	0.62

[a] See Fig. 1 for a guide to peptoid monomers.
[b] MW, molecular weight.
[c] ACN, acetonitrile; RP-HPLC, reverse-phase high-performance liquid chromatography.
[d] Log $D_{7.4}$, log (concentration of the solute in octanol/concentration of the solute in water) at pH 7.4.
[e] HD_{10} and HD_{50}, 10% and 50% hemolytic doses, respectively.
[f] Selectivity ratio (SR) = HD_{10}/*B. subtilis* MIC.
[g] ND, not determined.

TABLE 2. Broad-spectrum antibacterial activity of pexiganan and selected ampetoids against biosafety level 2 (BSL2) and BSL3 pathogenic bacteria

Strain	Gram staining	MICs (μg/ml) of:		
		Pexiganan	Peptoid 1	*N*tridec-1_{4mer}
Proteus vulgaris ATCC 49132	−	32.0	40.0	43.0
Pseudomonas aeruginosa ATCC 27853	−	4.0	10.0	10.8
Proteus mirabilis ATCC 35659	−	>128	>160	172
Klebsiella pneumoniae ATCC 33495	−	8.0	20.0	10.8
Enterobacter aerogenes ATCC 35029	−	32.0	20.0	>172
Escherichia coli ATCC 25922	−	8.0	5.0	10.8
Serratia marcescens ATCC 13880	−	>128	160	172
Staphylococcus aureus ATCC 29213	+	32.0	5.0	5.4
Staphylococcus aureus VAN1[a]	+	16.0	5.0	5.4
Staphylococcus aureus VAN2[a]	+	8.0	5.0	5.4
Staphylococcus aureus NRS100 (COL)	+	16.0	5.0	5.4
Staphylococcus aureus NRS119	+	64.0	5.0	5.4
Staphylococcus aureus NRS120	+	64.0	10.0	5.4
Enterococcus faecalis ATCC 29212	+	32.0	5.0	10.8
Enterococcus faecalis 99[a]	+	128	10.0	21.6
Enterococcus faecium 106[a]	+	4.0	5.0	5.4

[a] Vancomycin resistant.

spectrum antimicrobial activity of our previously reported antimicrobial peptoids but with substantially lower molecular weights and improved selectivity (6, 26). This approach will be useful in designing future peptoid and other peptidomimetic compounds with therapeutic potential against bacterial and fungal infections.

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