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REVIEW

Peptoids and polypeptoids: biomimetic and bioinspired materials for biomedical applications

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Abstract As material chemists and engineers aim to improve the properties of macromolecules for advanced biomedical applications, considerable attention has been paid to new classes of biomimetic polymers such as polypeptoids. Peptoid polymers can be synthesized from a wide variety of chemically diverse building blocks to create a broad family of functionally diverse materials. These materials have been shown to have a wide variety of biological activities and promising attributes. The ability to mimic nature's self-organization has become important in the area of biomaterials science. In this short colloquy, we provide an overview of the chemistry of peptoid/peptoid polymers including several applications. The discovery of few remarkable peptoids/polypeptoids of biological interest outlined over the past few decades will be discussed.

Keywords Biomedical · Bioinspired · Biomimetic · Nanomaterials · Peptoids · Peptoid nanosheets

Introduction

Today, to improve naturally occurring biomaterials, material chemists have been developing efficient methods to study biomimetic polymers [1, 2]. Advance materials must be developed to achieve the potential applications in the field of biomaterials science [3, 4]. One class of biomimetic polymer of particular interest is called peptoids, or N-substituted glycines [5] which have found many biomedical

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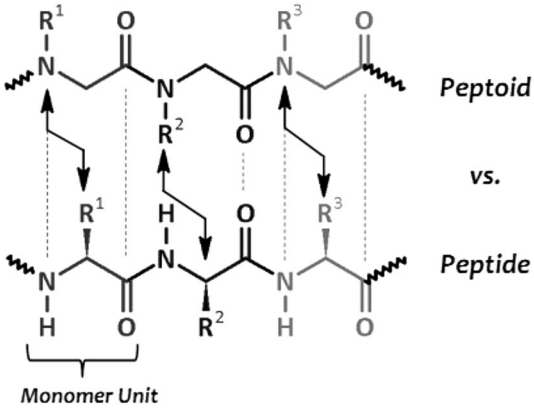

Fig. 1 Chemical structure comparison of peptide and peptoid

applications. Peptoids can be synthesized very efficiently by solid-phase synthesis, and combinatorial libraries were readily produced and screened to afford a novel set of active scaffolds in the early 1990s [6–8] as a modular approach to the discovery of novel drugs [9]. A desirable feature of these biomimetic heteropolymers is that they can be synthesized with defined monomer sequences that resist proteolysis [10–13]. Peptoids have also been shown to have antibacterial properties and clinical promise relative to those of natural peptides [14–17].

Peptoids are polymers of N-substituted glycines and are structural isomers of natural peptides. The side chains are attached to the α-carbon instead of the backbone of amide nitrogen (Fig. 1). They are prepared by the solid-phase submonomer method from primary amines, and their synthesis has been fully automated using simple adaptation of commercial peptide synthesizers [18, 19].

Recent reviews on peptoids highlight the scope and applications of highly customizable peptidomimetic macromolecules with many cited references [20–22]. The pioneering works of Bartlett and co-workers in 1992 reported the development of a combinatorial array of N-substituted glycine oligomers by peptidomimetic protocols. So, one can easily notice the booming progress in the development of monomeric scaffolds and this contributed to the exponential development of protected achiral N-substituted glycine monomers.

Background

Peptoid synthesis

The regioisomerization of peptides essentially affords a new class of peptidomimetics, called peptoids [6]. Peptoids are achiral, since the side chains are appended to the amide nitrogen rather than α-carbon. Peptoids of the defined sequence are prepared by the solid-phase "sub-monomer" method, in which bromoacetic acid and *N*,*N*′-diisopropylcarbodiimide (DIC) were employed to accomplish the acylation step, followed by nucleophilic displacement of bromine with a primary

amine. Consequently, quite diverse polypeptoid sequences can be developed by means of typical primary amines in successful iteration of the displacement reaction step. Rink amide resins are often employed, resulting in the release of peptoid as a C-terminal amide. The final cleavage step is accomplished using trifluoroacetic acid (TFA)-mediated special cocktails [23].

Synthetic strategies for peptoid construction

The technical interest in the developed solid-phase submonomer method by Zuckermann et al. has been significant with automated combinatorial synthetic procedure [7], in which chemically diverse peptoid libraries can be constructed effectively by iterative bromoacetylation and amination reactions. The search for alternative strategies is beneficial to reduce the reaction time and competent yields. This has led to the development of microwave-assisted solid-phase synthesis of peptoids [24–26]. Current synthetic approaches allow for the facile insertion of pendant groups exhibiting various chemical moieties. By the chemical functionality of the side chain moieties, it is quite possible to design peptoid heteropolymers, possessing structural diversity with unique chemical features. Constrained cyclic peptoids are also conformationally designed by efficient submonomer methodology and followed by cyclization in the solution phase [27]. Classic synthesis of cyclic peptoids relies on the simple strategic adaptation of combinatorial chemistry by high-throughput screening of linear peptoids [28]. Alternatively, peptoids are synthesized from solution-phase technique with limited sequential control of <10 residues [29] and, conversely, *N*-carboxyanhydride (NCA) is a more convenient precursor for peptoids. In this case, high degrees of polymerization can be achieved by ring opening polymerization with low sequence precision control [30–33]. Combinatorial peptoid array has been developed by the photolithographic technique using photolabile synthons for protein binding agents and this anticipated the protein ligand discovery [34]. Surprisingly, biosynthetic protocol involving the synthesis of peptoid–peptide hybrids with linear and cyclic scaffolds was programmed by mRNA and practically reported recently [35].

Customized biomedical applications of peptoids

Bioactive peptoids were discovered by rational design using molecular modeling and developed by either individually or in parallel focused libraries. Peptoids with defined structures seem to possess superior activities and new applications have emerged. The synthesis of hybrid cyclic peptoids has been emphasized in terms of molecular recognition, drug delivery and catalysis. However, solid-state assembly of free and metal coordination provide competing inter-annular hydrogen bond interactions, leading either to a T-shape or to a tubular arrangement of the peptoid macrocycles, and Hirshfeld surfaces and fingerprint plots were generated [36]. The choice of side chain functionalities plays a vital role in the construction of attractive supramolecular architectures. Also, it decides the diverse solid-state properties and conformational flexibility of cyclic α-peptoids [37]. The inter- and intramolecular

cyclization of *N*-(2-aminoethyl)glycine monomers, comprising *N*-alkyl and *N*-acyl substituents, affords stable 6- and 12-membered cyclic products. These libraries can be effectively used as potential candidates in enhancing the autophagic degradation of cargo in a live cell model [28, 38]. N-substituted-β-aminopropionic acid oligomers or β-peptoids were initially reported by Hamper et al. [39] by solid-phase methodology. Further, this was preceded by Roy et al. [40] to achieve β-peptoid macrocycles with multimeric ligation of bioactive ligands. Their effective functionalization was achieved by click chemistry synthetic route. Recent advances have begun to address the issue of cyclization methodology to attain macrocyclic peptoids. This has led to the suggestion that head-to-tail macrocyclization and ring closing metathesis approaches were effective for assembling the cyclic peptoids [41, 42]. Based on their relationship with side chain chemistries, Huang et al. suggested that oligomeric peptoids bearing a cationic nature with hydrophobic side chains showed potent antimicrobial activities against Gram-negative *Escherichia coli* (*E. coli*), Gram-positive *Staphylococcus aureus* (*S. aureus*) and *Bacillus subtilis* (*B. subtilis*). Peptoid sequences after head-to-tail macrocyclization mode interestingly showed enhanced antibacterial activity with increasing hydrophobic domains.

A minimum inhibitory concentration (MIC) value of cyclic decapeptide gramicidin S (CGS) for *B. subtilis* is 2 and 15.6 μg mL^{-1} for *E. coli* and *S. aureus* (see Fig. 2 for chemical structures and Table 1 for MIC values). Moderate activity with MIC <100 μgmL^{-1} was depicted by L3, L8 and C3. Effective activity was perceived by C8, cyclic peptoid decamer, with MIC values of 0.5 μgmL^{-1} for *B. subtilis*, and 7.8 μg mL^{-1} for *E. coli* and *S. aureus*, whereas the linear version of gramicidin S (LGS) showed 7.8 μg mL^{-1} for *B. subtilis* and 125 μg mL^{-1} *E. coli* and *S. aureus* [43]. The MIC values are remarkably better than oxazoline-based oligomers (pseudo peptides) and quaternary ammonium/phosphonium polymers [44, 45]. The inherent structural tendency, cellular permeability [46] and multiple binding sites of cyclic peptoids are extremely useful and can be employed for the

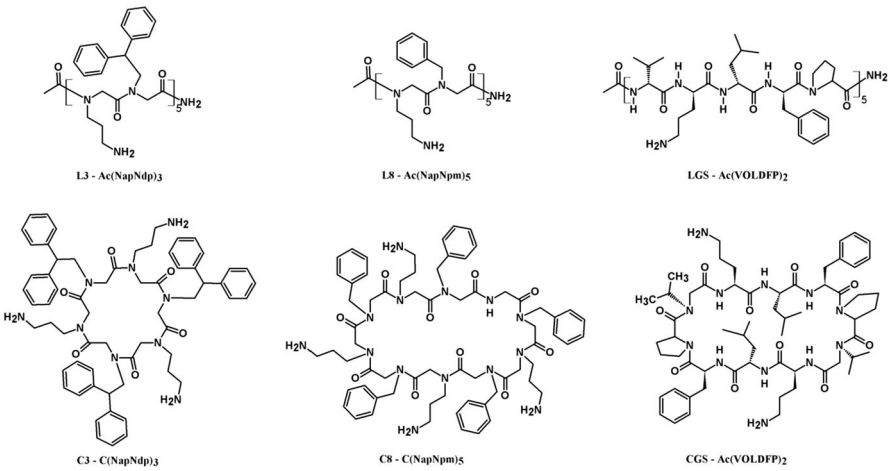

Fig. 2 Structures of selected linear and cyclic peptides and peptoid sequences [43]

Table 1 Antimicrobial activities of linear and cyclic peptoids [43]

Code	Peptoid sequence[a]	MIC (μg mL^{-1})[b]		
		B. subtilis	*E. coli*	*S. aureus*
L3	$Ac(NapNdp)_3$	1	15.6	15.6
L8	$Ac(NapNpm)_5$	15.6	31.3	62.5
LGS	$Ac(VOLDFP)_2$	7.8	125	125
C3	$C(NapNdp)_3$	1	15.6	7.8
C8	$C(NapNpm)_5$	0.5	7.8	7.8
CGS	$C(VOLDFP)_2$	2	15.6	15.6

[a] Prefixes Ac and C refer to N-acetylated linear and cyclic sequences, respectively

[b] Minimum inhibitory concentrations against *B. subtilis*, *E. coli* and *S. aureus*

metal–organic framework (MOF) structures to develop biomimetic materials and three-dimensional solid-state supramolecular assemblies.

Peptoids with more hydrophilicity display the best cell permeability. In addition, peptoids with hydrophobic moieties, usually aromatics, cannot differentiate between the binding domains of different proteins [47]. Kodadek and co-workers comprehensively performed the peptoid cellular permeability criterion. By employing the split-pool method, a library of more than 350 peptoids and α-peptide tetramers was prepared and analyzed to generate structure–property relationships and their relative cell permeability. From the observations, the average cell permeability of the peptoids was twice that of the α-peptides [86]. As shown by the extensive research on the construction of a variety of peptoids, peptoid nucleic acid precursors bearing adenine, guanine and thymine units to nitrogen by flexible ethylene bridge was achieved by the Mitsunobu reaction. The deprotection of these amino acids affords protected dipeptoids [73]. In the recent past, Park and Kwon explored the pharmacokinetic properties of new combinatorial series of linear and cyclic peptoid analogs. Also, they showed the biological activities by blocking the interaction between apolipoprotein E and amyloid-β and proposed these therapeutic peptoid series for the treatment of Alzheimer's disease [48]. Incorporation of a zinc binding region into the peptoid two-helix bundle was implemented by Zuckermann and colleagues in the early 2008 [49]. Stabilizing characteristics of native protein structures by zinc showed catalytic enzyme cofactor activities, which influenced the choice of zinc-binding motifs. These developed peptoids would only be capable of binding with the zinc, when suitably folded into the helix bundle structure. The thiols and imidazole groups were incorporated into the helical segments of the aforementioned peptoid, expecting the zinc to stabilize the folded state of the two-helix bundles by holding the helical segments in close proximity. The authors analyzed the ability of peptoids to bind with the zinc and the structure alterations in the presence of zinc [50].

Peptoids with heterocyclic pendants show their possible applications in catalysis and materials science. Primary amines derived from imidazole, pyridine and other heterocyclic synthons in the preparation of novel peptoids were gracefully illustrated by the SPOT technique. The SPOT concept was performed on the cellulose membrane strips [51–53]. These heteroaromatic groups that are incorporated act as multidentate ligands in the peptoid chain. These ligands enable their use

in metal coordination and are popularly known as metallopeptoids [54]. Maria and Galia [55] suggested that the insertion of the chiral hydrophilic "(S)-(1)-1-methoxy-2-propylamine" group within the peptoid sequences offers water solubility. These water-soluble functional peptoids [56] emphasize their applications in sensors and catalysis. Inevitably, motivation of the significant antiproliferative active peptoids without heteroaromatic side groups showed active cytotoxic efficacy against human neoplastic cell lines [57]. Recently, a compelling approach has been put forward for the stability of nanoparticles under biological assembly conditions using small peptoids [58]. These small peptoids were projected on the development of fluorescent pH sensors. [59].

In contrast to the amino acid derivatives and cyclic dipeptides, "*N*-alkyl urea peptoids", as they share some structural similarities with "*N*-acyl glycine oligomers", demonstrated the synthesis of soft materials and served as ideal candidates for structure/property relationship studies with peptoids. Organogelators with diverse functional *N*-alkyl groups afford fiber-like aggregates and can be attained by incorporating ureidopyrimidinone (UPy) group and *N*-alkyl urea peptoid oligomers into the polymeric gels [60]. The significant work of the Wu and Mangunuru research teams pointed to the importance of peptoid hydrogels. They revealed various protected glucosamine moieties along with aryl functional groups in the peptoid side chains. Also, the self-assembling properties of these new classes of tripeptoids and the in vivo stability of the peptoid–peptide molecular hydrogel conjugates are highlighted [61, 62]. These gelators are extensively studied because of their consolidation properties in tissue engineering and drug delivery applications. The design of specific protein binding to the terminal peptoid sequence proved the formation of polyelectrolyte amphiphiles. These amphiphiles form self-assembly systems and act as nano-sized carriers for lipophilic drug delivery [63, 64].

Nacre mimetic materials are considerably more complicated to synthesize than the synthetics [65]. They form the bio analogs within the fixed dimensions to afford hybrid organic/inorganic composite materials in the order of nanoscale range [66, 67]. The incorporation of calcium carbonate ($CaCO_3$) to both the soluble synthetic polymer films and insoluble hybrid polymeric matrices afford thin solid films. These mineralized films have been demonstrated to be a model for explicative studies on the concept of biomineralization [68–70]. Peptoid nanosheets are highly stable nanoarchitectures with bilayered hybrid structures of thickness ≈ 3 nm and lateral dimensions varying between few hundreds of micrometers [64, 71]. The use of peptoid-based self-assembling bioinspired nanomaterials have proven to be a reliable approach in the creation of functional and biomimetic materials. Directed assembly process has the potential to develop free-floating two-dimensional nanostructured material sheets [13]. These sheets are formed relatively at lower activation energy. The compression of loop-forming peptoid domains is confined in phases such as air–water or oil–water interphases to assemble into nanosheets (Fig. 3). These fundamental findings gathered interest in designing antibody mimetic peptoid nanosheets [19]. These nanosheets are an emerging class of two-dimensional biomimetic materials with customizable properties.

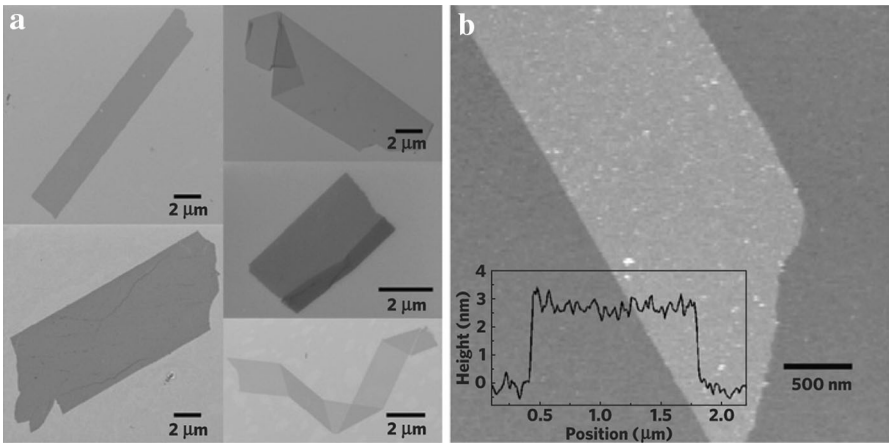

Fig. 3 Imaging of 2D crystalline sheets assembled from periodic amphiphilic peptoid polymers. In typical conditions, 0.1 mM of $(Nae–Npe)_{18}$ and $(Nce–Npe)_{18}$ were mixed in Tris–HCl buffer (pH 9.0, 100 mM). **a** SEM images of sheets on Si substrate. **b** Height-mode AFM image of a sheet (*Z* range 20 nm) [64]

More recently, peptoid nanosheets are mineralized with $CaCO_3$ by plunging the nanosheets in a prescribed concentration of calcium chloride ($CaCl_2$) solution and slowly diffusing carbon dioxide (CO_2) into the solution to afford the mineralized nanosheets [71]. It is absolutely vital to explore these fabricated biomimetic materials with specific dimensions for tissue engineering applications [72]. The hydrophilic and zwitterionic surface morphology of these two-dimensional structures make them free-floating suspensions in solution. Due to the exceptional stability of peptoid nanosheets and their ease of surface functionalization, gold-ornamented peptide–peptoid hybrid analogs can be designed [13, 19]. The resulting applications range from clinical to materialistic interests by embedding bioactive nanostructures on these flexible well-defined peptoid nanosheets.

Summary and outlook

Polypeptoids are exemplary non-natural polymers projected to mimic the functions of natural peptides or proteins. These pseudo peptides are tuned structurally to mimic the significant cooperative properties by altering the side chain chemistries and building subunits. Subsequent modification of the alkyne side chain of poly(*N*-propargyl glycine) can readily serve the modular platform for the production of pseudo peptide ionic liquids and graft copolymers [74, 75]. These bioinspired materials demonstrate a capability for folding, self-assembly and specific biorecognition. In the course of development to get the protein-like properties with narrow polymer molecular weight distributions, helical polymers have been designed by introducing chirality into monomer side chains [76]. Side chain groups with aromatic and heterocyclic moieties [77] are accountable for change in optical activity to target ribonucleic acid (RNA) [78, 79].

Designing the biomimetic polymers for controlled biomineralization is a very challenging task. One way to ease this claim is to develop a peptoid library with the preferred functional side chain groups [72, 80]. Effective pharmacokinetic activity and biological activities with increased resistance to enzymatic degradation is often shown by cyclic peptoids. They possess constrained flexibility compared with the linear ones [48]. Oligopeptoids predominantly composed of "(S)-*N*-(1-phenylethyl)glycine" residues are generally water insoluble. The flexible hydrophilic carboxy phenylethyl side chains are anticipated to provide both water solubility and structure-inducing elements to form stable helical structures resembling polyproline I type of helix [81, 82]. Peptide–peptoid hybrids (peptomers) with preferred active sites and functional groups specifically activate the melanocortin 4-receptor with improved enzymatic stability and intestinal permeability [83]. Pharmaceutically relevant heterocyclic side chains such as pyridine, pyrazine, imidazole and quinolone pendant moieties can be incorporated efficiently by the SPPS methodology, though the heterocyclic nitrogen containing side chain is present within the peptoid [84].

Today, a variety of peptidomimetic oligomeric scaffolds are being explored to show significant applications ranging from medicinal chemistry to materials science. Researchers are incorporating chemically diverse pendant groups to the peptoid sequence to study the formation of stable self-assemblies and biomimetic folded structures. Sequence specificity has been illustrated by the insertion of clinically bioactive complex heterocycles with variable polysaccharide mimic side chains to afford peptoid combinatorial library for biomedically relevant studies [83, 84]. On the contrary, the applications of peptoid nanoarchitectures have become more prevalent. Peptoid nanosheets and nanotubes have gained great attention recently [13, 19, 71, 87], because it has been realized that the efficacy of these designs provides vast contributions to the biomaterials and biomedical science [88]. Owing to their excellent biocompatibility and biofunctionality, peptoid polymers with specific sequential order have substituted the thought of designing biocompatible implants from the idea of biomimetics [15, 88]. As peptoids display potent antibacterial and antifouling properties [89], these are developed according to clinical needs [16]. To gain insight into the antibiotic properties of the peptoid synthetics, Brauer et al. proposed a design strategy, in which 1,3-diyne-linked peptoids were developed by reliable sequential Ugi-4CR/Glaser coupling approach [90–93].

Polypeptoids are a highly demanding class of biorelevant polymers and have great potential toward biomedical applications [85, 86, 88, 94]. In relation to their peptide predecessors, they promise to be biocompatible and degradable, but yet enzymatically resistant. Fundamental investigations illustrated that polypeptoids undergo phase transformations in response to temperature and have thermo-processability potential [33, 92]. These features would allow the designing of polymer–drug conjugates and composite biomaterials. Furthermore, the functional allyl or propargyl side-chain polypeptoids [75] allow cross-linking and surface modifications, facilitating the design of mechanically strong materials with biologically interacting molecules. In all these pursuits, there are many challenges that need to be overcome and further research is required prior to the targeted design

of biomaterials. The fundamental work described herein was driven by the preceding practical prospective of these polymers. Undoubtedly, these developments will help both synthetic and material chemists a great deal in presenting unexplored possible biobeneficial significance.

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References

1. Wegst UGK, Bai H, Saiz E, Tomsia AP, Ritchie RO (2015) Bioinspired structural materials. Nat Mater 14:23–36
2. Trabocchi A, Guarna A (2014) Chapter,1 peptidomimetics in organic and medicinal chemistry: the art of transforming peptides in drugs. John Wiley & Sons Ltd, Chichester, pp 1–17
3. Jung JP, Gasiorowski JZ, Collier JH (2010) Fibrillar peptide gels in biotechnology and biomedicine. Biopolymers (Pept Sci) 94:49–59
4. Fisher OZ, Khademhosseini A, Langer R, Peppas NA (2010) Bioinspired materials for controlling stem cell fate. Acc Chem Res 43:419–428
5. Petros RA, DeSimone JM (2010) Strategies in the design of nanoparticles for therapeutic applications. Nat Rev Drug Discov 9:615–627
6. Simon RJ, Kania RS, Zuckermann RN, Huebner VD, Jewell DA, Banville S, Ng S, Wang L, Rosenberg S, Marlowe CK, Spellmeyer DC, Tan RY, Frankel AD, Santi DV, Cohen FE, Bartlett PA (1992) Peptoids: a modular approach to drug discovery. Proc Natl Acad Sci USA 89:9367–9371
7. Zuckermann RN (2011) Peptoid origins. Biopolymers (Pept Sci) 96:545–555
8. Kirshenbaum K, Barron AE, Goldsmith RA, Armand P, Bradley EK, Truong KTV, Dill KA, Cohen FE, Zuckermann RN (1998) Proc Natl Acad Sci USA 95:4303–4308
9. Zuckermann RN, Kerr JM, Kent SBH, Moos WH, Simon RJ, Goff DA (1995) Synthesis of N-substituted oligomers. US Patent Number: US 5831005
10. Miller SM, Simon RJ, Ng S, Zuckermann RN, Kerr JM, Moos WH (1994) Proteolytic studies of homologous peptide and N-substituted glycine peptoid oligomers. Bioorg Med Chem Lett 4:2657–2662
11. Miller SM, Simon RJ, Ng S, Zuckermann RN, Kerr JM, Moos WH (1995) Comparison of the proteolytic susceptibilities of homologous L-amino acid, D-amino acid, and N-substituted glycine peptide and peptoid oligomers. Drug Dev Res 35:20–32
12. Kruijtzer JAW, Hofmeyer LJF, Heerma W, Versluis C, Liskamp RMJ (1998) Solid-phase syntheses of peptoids using Fmoc-protected N-substituted glycines: the synthesis of (retro)peptoids of leu-enkephalin and substance P. Chem Eur J 4:1570–1580
13. Olivier GK, Cho A, Sanii B, Connolly MD, Tran H, Zuckermann RN (2013) Antibody-mimetic peptoid nanosheets for molecular recognition. ACS Nano 7:9276–9286
14. Statz AR, Park JP, Chongsiriwatana NP, Barron AE, Messersmith PB (2008) Surface-immobilised antimicrobial peptoids. Biofouling 24:439–448
15. Lau KHA (2014) Peptoids for biomaterials science. Biomater Sci 2:627–633
16. Goodson B, Ehrhardt A, Ng S, Nuss J, Johnson K, Giedlin M, Yamamoto R, Moos WH, Krebber A, Ladner M, Giacona MB, Vitt C, Winter J (1999) Characterization of novel antimicrobial peptoids. Antimicrob Agents Chemother 43:1429–1434
17. Ng S, Goodson B, Ehrhardt A, Moos WH, Siani M, Winter J (1999) Combinatorial discovery process yields antimicrobial peptoids. Bioorg Med Chem 7:1781–1785
18. Kirshenbaum K, Zuckermann RN, Dill KA (1999) Designing polymers that mimic biomolecules. Curr Opin Struct Biol 9:530–535

19. Robertson EJ, Olivier GK, Qian M, Proulx C, Zuckermann RN, Richmond GL (2014) Assembly and molecular order of two-dimensional peptoid nanosheets through the oil–water interface. PNAS USA 111:13284–13289
20. Creighton CJ, Zapf CW, Bu JH, Goodman M (1999) Solid-phase synthesis of pyridones and pyridopyrazines as peptidomimetic scaffolds. Org Lett 1:1407–1409
21. Nakayama K, Kawato HC, Inagaki H, Ohta T (2001) Novel peptidomimetics of the antifungal cyclic peptide rhodopeptin: design of mimetics utilizing scaffolding methodology. Org Lett 3:3447–3450
22. Gangloff N, Ulbricht J, Lorson T, Schlaad H, Luxenhofer R (2016) Peptoids and polypeptoids at the frontier of supra- and macromolecular engineering. Chem Rev 116(4):1753–1802
23. King DS, Fields CG, Fields GB (1990) A cleavage method which minimizes side reactions following Fmoc solid phase peptide synthesis. Int J Peptide Protein Res 36:255–266
24. Gorske BC, Jewell SA, Guerard EJ, Blackwell HE (2005) Expedient synthesis and design strategies for new peptoid construction. Org Lett 7:1521–1524
25. Seo J, Michaelian N, Owens SC, Dashner ST, Wong AJ, Barron AE, Carrasco MR (2009) Chemoselective and microwave-assisted synthesis of glycopeptoids. Org Lett 11:5210–5213
26. Olivos HJ, Alluri PG, Reddy MM, Salony D, Kodadek T (2002) Microwave-assisted solid-phase synthesis of peptoids. Org Lett 4:4057–4059
27. Shin SBY, Yoo B, Todaro LJ, Kirshenbaum K (2007) Cyclic peptoids. J Am Chem Soc 129:3218–3225
28. Rajasekhar K, Narayanaswamy N, Mishra P, Suresh SN, Manjithaya R, Govindaraju T (2014) Synthesis of hybrid cyclic peptoids and identification of autophagy enhancer. Chem Plus Chem 79:25–30
29. Hjelmgaard T, Faure S, Caumes C, Santis ED, Edwards AA, Taillefumier C (2009) Convenient solution-phase synthesis and conformational studies of novel linear and cyclic α,β-alternating peptoids. Org Lett 11:4100–4103
30. Darensbourg DJ, Phelps AL, Gall LN, Jia L (2004) Mechanistic studies of the copolymerization reaction of aziridines and carbon monoxide to produce poly-β-peptoids. J Am Chem Soc 126:13808–13815
31. Jia L, Sun HL, Shay JT, Allgeier AM, Hanton SD (2002) Living alternating copolymerization of N-alkylaziridines and carbon monoxide as a route for synthesis of poly-β-peptoids. J Am Chem Soc 124:7282–7283
32. Luxenhofer R, Fetsch C, Grossmann A (2013) Polypeptoids: a perfect match for molecular definition and macromolecular engineering? J Polym Sci Part A Polym Chem 51:2731–2752
33. Zhang DH, Lahasky SH, Guo L, Lee CU, Lavan M (2012) Polypeptoid materials: current status and future perspectives. Macromolecules 45:5833–5841
34. Li S, Bowerman D, Marthandan N, Klyza S, Luebke KJ, Garner HR, Kodadek T (2004) Photolithographic synthesis of peptoids. J Am Chem Soc 126:4088–4089
35. Kawakami T, Murakami H, Suga H (2008) ribosomal synthesis of polypeptoids and peptoid–peptide hybrids. J Am Chem Soc 130:16861–16863
36. Tedesco C, Erra L, Izzo I, Riccardis FD (2014) Solid state assembly of cyclic α-peptoids. Cryst Eng Comm 16:3667–3687
37. Sun Y, Du J, Wang Y, Wu S (2010) Theoretical binding affinities and spectra of complexes formed by a cyclic β-peptoid with amino acids. Chem Pap 64:515–522
38. Stolz A, Ernst A, Dikic I (2014) Cargo recognition and trafficking in selective autophagy. Nat Cell Biol 16:495–501
39. Hamper BC, Kolodziej SA, Scates AM, Smith RG, Cortez E (1998) Solid phase synthesis of β-peptoids: N-substituted β-aminopropionic acid oligomers. J Org Chem 63:708–718
40. Roy O, Faure S, Thery V, Didierjean C, Taillefumier C (2008) Cyclic β-peptoids. Org Lett 10:921–924
41. Culf AS, Čuperlović-Culf M, Léger DA, Decken A (2014) Small head-to-tail macrocyclic α-peptoids. Org Lett 16:2780–2783
42. Khan SN, Kim A, Grubbs RH, Kwon Y-K (2011) Ring-closing metathesis approaches for the solid-phase synthesis of cyclic peptoids. Org Lett 13:1582–1585
43. Huang ML, Shin SBY, Benson MA, Torres VJ, Kirshenbaum K (2012) A comparison of linear and cyclic peptoid oligomers as potent antimicrobial agents. Chem Med Chem 7:114–122
44. Martins C, Correia VG, Aguiar-Ricardo A, Cunha Â, Moutinho MGM (2015) Antimicrobial activity of new green-functionalized oxazoline-based oligomers against clinical isolates. SpringerPlus 4:382

45. Xue Y, Xiao H, Zhang Y (2015) antimicrobial polymeric materials with quaternary ammonium and phosphonium salts. Int J Mol Sci 16(2):3626–3655
46. Cho S, Choi J, Kim A, Lee Y, Kwon Y-U (2010) Efficient solid-phase synthesis of a series of cyclic and linear peptoid-dexamethasone conjugates for the cell permeability studies. J Comb Chem 12:321–326
47. Izzo I, Ianniello G, Cola CD, Nardone B, Erra L, Vaughan G, Tedesco C, Riccardis FD (2013) Structural effects of proline substitution and metal binding on hexameric cyclic peptoids. Org Lett 15:598–601
48. Park S, Kwon Y-U (2015) Facile solid-phase parallel synthesis of linear and cyclic peptoids for comparative studies of biological activity. ACS Comb Sci 17:196–201
49. Lee B-C, Chu TK, Dill KA, Zuckermann RN (2008) Biomimetic nanostructures: creating a high-affinity zinc-binding site in a folded nonbiological polymer. J Am Chem Soc 130:8847–8855
50. Burkoth TS, Beausoleil E, Kaur S, Tang D, Cohen FE, Zuckermann RN (2002) Toward the synthesis of artificial proteins: the discovery of an amphiphilic helical peptoid assembly. Chem Biol 9:647–654
51. Frank R (1992) Spot-synthesis: an easy technique for the positionally addressable, parallel chemical synthesis on a membrane support. Tetrahedron 48:9217–9232
52. Heine N, Ast T, Schneider-Mergener J, Reineke U, Germeroth L, Wenschuh H (2003) Synthesis and screening of peptoid arrays on cellulose membranes. Tetrahedron 59:9919–9930
53. Maayan G, Yoo B, Kirshenbaum K (2008) Heterocyclic amines for the construction of peptoid oligomers bearing multi-dentate ligands. Tetrahedron Lett 49:335–338
54. Maayan G, Ward MD, Kirshenbaum K (2009) Metallopeptoids. Chem Commun (1):56–58. doi:10.1039/B810875G
55. Baskin M, Maayan G (2015) Water-soluble chiral metallopeptoids. Biopolymers 104:577–584
56. Sanborn TJ, Wu CW, Zuckermann RN, Barron AE (2002) Extreme stability of helices formed by water-soluble poly-N-substituted glycines (polypeptoids) with α-chiral side chains. Biopolymers 63:12–20
57. Mas-Moruno C, Cruz LJ, Mora P, Francesch A, Messeguer A, Pérez-Payá E, Albericio F (2007) Smallest peptoids with antiproliferative activity on human neoplastic cells. J Med Chem 50:2443–2449
58. Robinson DB, Buffleben GM, Langham ME, Zuckermann RN (2011) Stabilization of nanoparticles under biological assembly conditions using peptoids. Biopolymers (Pept Sci) 96:669–678
59. Fuller AA, Holmes CA, Seidl FJ (2013) A fluorescent peptoid pH-sensor. Biopolymers (Pept Sci) 100:380–386
60. Chen X, Fei P, Cavicchi KA, Yang W, Ayres N (2014) The poor solubility of ureidopyrimidinone can be used to form gels of low molecular weight *N*-alkyl urea oligomers in organic solvents. Colloid Polym Sci 292:477–484
61. Mangunuru HPR, Yang H, Wang GJ (2013) Synthesis of peptoid based small molecular gelators by a multiple component reaction. Chem Commun 49:4489–4491
62. Wu ZD, Tan M, Chen XM, Yang ZM, Wang L (2012) Molecular hydrogelators of peptoid–peptide conjugates with superior stability against enzyme digestion. Nanoscale 4:3644–3646
63. Domurado D, Vert M (2007) Bioresorbable polyelectrolyte amphiphiles as nanosized carriers for lipophilic drug solubilization and delivery. J Biomater Sci Polym Ed 18:287–301
64. Nam KT, Shelby SA, Choi PH, Marciel AB, Chen R, Tan L, Chu TK, Mesch RA, Byoung-Chul L, Connolly MD, Kisielowski C, Zuckermann RN (2010) Free-floating ultrathin two-dimensional crystals from sequence-specific peptoid polymers. Nat Mater 9:454–460
65. Tang Z, Kotov NA, Magonov S, Ozturk B (2003) Nanostructured artificial nacre. Nat Mater 2:413–418
66. Bouville F, Maire E, Meille S, Van de Moortèle B, Stevenson AJ, Deville S (2014) Strong, tough and stiff bioinspired ceramics from brittle constituents. Nat Mater 13:508–514
67. Kou L, Gao C (2013) Bioinspired design and macroscopic assembly of poly(vinyl alcohol)-coated graphene into kilometers-long fibers. Nanoscale 5:4370–4378
68. Tanaka Y, Nemoto T, Naka K, Chujo Y (2000) Preparation of $CaCO_3$/polymer composite films via interaction of anionic starburst dendrimer with poly(ethylenimine). Polym Bull 45:447–450
69. Achal V, Mukherjee A, Kumari D, Zhang Q (2015) Biomineralization for sustainable construction—a review of processes and applications. Earth Sci Rev 148:1–17
70. Dhami NK, Reddy MS, Mukherjee A (2013) Biomineralization of calcium carbonates and their engineered applications: a review. Front Microbiol 4:314

71. Jun JMV, Altoe MVP, Aloni S, Zuckermann RN (2015) Peptoid nanosheets as soluble, two-dimensional templates for calcium carbonate mineralization. Chem Commun 51:10218–10221
72. Liu X, Ma Y, Zhou Y, Pei C, Yin G (2013) A promising hybrid scaffold material: bacterial cellulose in-situ assembling biomimetic lamellar $CaCO_3$. Mater Lett 102–103:91–93
73. Wu Y, Ji-Cheng X, Liu J, You-Xing J (2001) Synthesis of N-Boc and N-Fmoc dipeptoids with nucleobase residues as peptoid nucleic acid monomers. Tetrahedron 57:3373–3381
74. Secker C, Robinson JW, Schlaad H (2015) Alkyne-X modification of polypeptoids. Eur Polym J 62:394–399
75. Caumes C, Roy O, Faure S, Taillefumier C (2012) The click triazolium peptoid side chain: a strong cis-amide inducer enabling chemical diversity. J Am Chem Soc 134:9553–9556
76. Okamoto Y, Nakano T, Habaue S, Shiohara K, Maeda K (1997) Synthesis and chiral recognition of helical polymers. J Macromol Sci Part A A34:1771–1783
77. Barron AE, Zuckermann RN (1999) Bioinspired polymeric materials: in-between proteins and plastics. Curr Opin Chem Biol 3:681–687
78. Norgren AS, Zhang S, Arvidsson PI (2006) Synthesis and circular dichroism spectroscopic investigations of oligomeric β-peptoids with α-chiral side chains. Org Lett 8:4533–4536
79. Kesavan V, Tamilarasu N, Cao H, Rana TM (2002) A new class of RNA-binding oligomers: peptoid amide and ester analogues. Bioconjugate Chem 13:1171–1175
80. Chun-Long C, Qi J, Zuckermann RN, DeYoreo JJ (2011) Engineered biomimetic polymers as tunable agents for controlling $CaCO_3$ mineralization. J Am Chem Soc 133:5214–5217
81. Shin SBY, Kirshenbaum K (2007) Conformational rearrangements by water-soluble peptoid foldamers. Org Lett 9:5003–5006
82. Wu CW, Kirshenbaum K, Sanborn TJ, Patch JA, Huang K, Dill KA, Zuckermann RN, Barron AE (2003) Structural and spectroscopic studies of peptoid oligomers with α-chiral aliphatic side chains. J Am Chem Soc 125:13525–13530
83. Ovadia O, Linde Y, Haskell-Luevano C, Dirain ML, Sheynis T, Jelinek R, Gilon C, Hoffman A (2010) The effect of backbone cyclization on PK/PD properties of bioactive peptide-peptoid hybrids: the melanocortin agonist paradigm. Bioorg Med Chem 18:580–589
84. Burkoth TS, Fafarman AT, Charych DH, Connolly MD, Zuckermann RN (2003) Incorporation of unprotected heterocyclic side chains into peptoid oligomers via solid-phase submonomer synthesis. J Am Chem Soc 125:8841–8845
85. Patch JA, Barron AE (2002) Mimicry of bioactive peptides via non-natural, sequence-specific peptidomimetic oligomers. Curr Opin Chem Biol 6:872–877
86. Zuckermann RN, Kodadek T (2009) Peptoids as potential therapeutics. Curr Opin Mol Ther 11:299–307
87. Vollrath SBL, Hu C, Bräse S, Kirshenbaum K (2013) Peptoid nanotubes: an oligomer macrocycle that reversibly sequesters water via single-crystal-to-single-crystal transformations. Chem Commun 49:2317–2319
88. Bong DT, Clark TD, Granja JR, Ghadiri MR (2001) Self-assembling organic nanotubes. Angew Chem Int Ed 40:988–1011
89. Lau KHA, Sileika TS, Park SH, Sousa AML, Burch P, Szleifer I, Messersmith PB (2015) Molecular design of antifouling polymer brushes using sequence-specific peptoids. Adv Mater Interfaces 2:1400225
90. Galetti MD, Cirigliano AM, Cabrera GM, Ramírez JA (2012) Multicomponent synthesis of acylated short peptoids with antifungal activity against plant pathogens. Mol Divers 16:113–119
91. Ghasemi E, Shahvelayati AS, Yavari I (2016) Ugi reaction of thiouridocarboxylic acids: a synthesis of thiourea–peptoids. Phosphorus Sulfur Silicon Relat Elem 191:746–750
92. Silva EHB, Emery FS, Ponte GD, Donate PM (2015) Synthesis of some functionalized peptomers via Ugi four-component reaction. Synth Commun 45:1761–1767
93. Brauer MCN, Filho RAWN, Westermann B, Heinke R, Wessjohann LA (2015) Synthesis of antibacterial 1,3-diyne-linked peptoids from an Ugi-4CR/Glaser coupling approach. Beilstein J Org Chem 11:25–30
94. Sun J, Zuckermann RN (2013) Peptoid polymers: a highly designable bioinspired material. ACS Nano 6:4715–4732