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A Multiple Multicomponent Approach to Chimeric Peptide–Peptoid Podands

Daniel G. Rivera,[a, b] Fredy León,[a] Odette Concepción,[b] Fidel E. Morales,[b] and Ludger A. Wessjohann*[a]

Abstract: The success of multi-armed, peptide-based receptors in supramolecular chemistry traditionally is not only based on the sequence but equally on an appropriate positioning of various peptidic chains to create a multivalent array of binding elements. As a faster, more versatile and alternative access toward (pseudo)peptidic receptors, a new approach based on multiple Ugi four-component reactions (Ugi-4CR) is proposed as a means of simultaneously incorporating several binding and catalytic elements into organizing scaffolds. By employing α-amino acids either as the amino or acid components of the Ugi-4CRs, this multiple multicomponent process allows for the one-pot assembly of podands bearing chimeric peptide–peptoid chains as appended arms. Tripodal, bowl-shaped, and concave polyfunctional skeletons are employed as topologically varied platforms for positioning the multiple peptidic chains formed by Ugi-4CRs. In a similar approach, steroidal building blocks with several axially-oriented isocyano groups are synthesized and utilized to align the chimeric chains with conformational constrains, thus providing an alternative to the classical peptido-steroidal receptors. The branched and hybrid peptide–peptoid appendages allow new possibilities for both rational design and combinatorial production of synthetic receptors. The concept is also expandable to other multicomponent reactions.

Keywords: multicomponent reactions · steroids · supramolecular chemistry · synthetic receptors · Ugi reaction

Introduction

The development of new strategies for the construction of synthetic receptors and ligands has attracted significant attention in the last decades. The creation of new, efficient complexing agents for ions or larger organic molecules is based on the concepts of either rational design[1] or on combinatorial methods.[2] Despite the immense progress achieved, both the binding prediction and the fast and efficient incorporation of multiple binding functionalities into recognition frameworks remain truly challenging. Most rapid and straightforward approaches toward synthetic receptors produce homo-oligomeric or highly repetitive compounds, usually suitable for binding either simple, achiral guests or spherical ions, but are in general ineffective for more complex substrates like small organic molecules or biomolecules. Indeed, selective and efficient recognition processes for these latter substrates require complex, multivalent receptors capable to exert biomimicry through a multifaceted binding behavior.[1,3,4] This concept has been successfully implemented by creating chimeric receptors, that is, multimotif entities capable to exert the recognition process based either on multivalent,[1] cooperative[3] or allosteric[4] effects derived from the simultaneous participation of hybrid organic or metallo-(bio)molecular frameworks. Nevertheless, the quest to achieve these remarkable hybrid entities always comprises very elaborate, stepwise syntheses that focus on the sequential incorporation of varied recognition or catalytic motifs, with the consequence of high cost or time owing to the long synthetic routes.

Accordingly, synthetic approaches that rapidly and efficiently generate complex multifunctional binding sites tailored for complex and chiral substrates are in high demand, for example, in the areas of catalyst and receptor design, because they are expected to increase the number of relevant hits. Owing to the unraveling way by which multicomponent reactions (MCRs) can simultaneously incorporate several chemical motifs into a single structure, their application in this field holds significant promise. Of special interest is the utilization of MCRs that either generate natural-like binding elements by themselves or allow for the efficient incorporation of these. This is the case with isonitrile-MCRs,[5] which are well-known for producing pseudo-peptidic (e.g., pep-

[a] Dr. D. G. Rivera, F. León, Prof. Dr. L. A. Wessjohann
Department of Bioorganic Chemistry
Leibniz Institute of Plant Biochemistry
Weinberg 3, 06120 Halle/Saale (Germany)
Fax: (+49) 345-5582-1309
E-mail: wessjohann@ipb-halle.de

[b] Dr. D. G. Rivera, O. Concepción, F. E. Morales
Center for Natural Products Research
Faculty of Chemistry, University of Havana
La Habana 10400 (Cuba)

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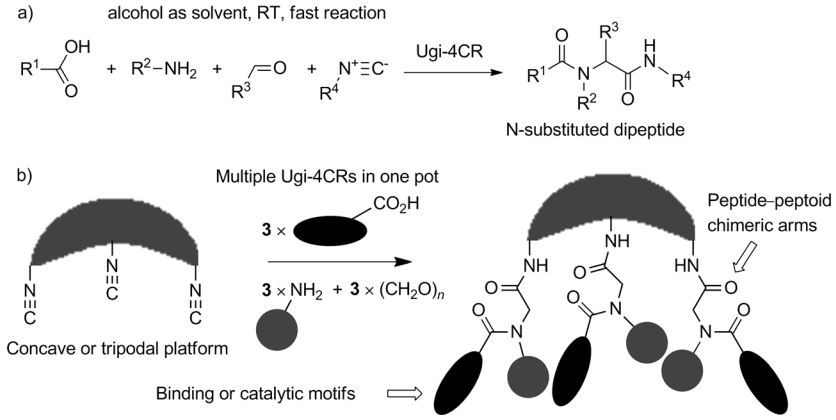
toids, depsipeptides) and peptidomimetic motifs (e.g., oxa-, thia- and tetrazoles, diketopiperazines) in a diversity-oriented manner.[6–8]

Here we report a completely new class of chimeric peptide–peptoid podands, produced by an isonitrile-MCR-based approach capable to assemble in one step several building blocks that can carry recognition and catalytic motifs. The multicomponent assembly process encompasses the use of threefold Ugi four-component reactions[8,9] (Ugi-4CRs) on polyfunctional, tripodal, and concave skeletons with known propensity to position binding functionalities in a preorganized form. As shown in Scheme 1 A, the simplest version of the Ugi-4CR comprises the one-pot condensation of a primary amine, an oxo compound, a carboxylic acid and an isonitrile to form a *N*-substituted dipeptide (a peptoid in the broad sense). When using amino acids either as the amino or carboxy components of this reaction, the chemical moiety formed can be regarded as a peptide–peptoid hybrid.[7,10] Peptoids are non-natural surrogates of peptides that contain the side-chain derivatization at the nitrogen of the amide instead of the α-carbon. They may mimic many of the well-known recognition and coordination properties of peptides, such as: the chelation of cations by the amide bonds and binding to neutral molecules by means of hydrogen bonding.[10] Scheme 1 B illustrates the prospect of the multiple multicomponent (mMCR) approach that produces multivalent frameworks by incorporating 10 building blocks in a single step. A key feature of this approach is the rapid access to a wide diversity of peptide–peptoid hybrid architectures by taking advantage of both the many commercial building blocks available with amino or carboxylic acid functions and the easy installation of isonitrile groups on readily available tripodal and concave scaffolds. Formaldehyde is commonly selected as oxo component with the aim to avoid the formation of diastereomers as well as to be firmly fixed to the definition of peptoids (i.e., *N*-substituted polyglycines as peptoids in the strictest sense).



Scheme 1. a) Ugi four-component reaction (Ugi-4CR). b) Approach to multivalent, hybrid podands and receptors by threefold Ugi-4CRs with the incorporation of 10 building blocks.

Results and Discussion

Previously we could demonstrate that multiple Ugi-4CRs allow rapid access to a plethora of macro(multi)cyclic architectures.[8,9] However, acyclic synthetic receptors can be more versatile than macrocycles in recognition studies of complex biomolecules,[2,11] mainly due to their easier accessibility and functionalization with multiple binding motifs. Dilution, pseudo-dilution, or long reaction times are not mandatory and their higher conformational freedom allows for more induced fits. In the following, this broader scope of multifold Ugi-4CRs in podand assembly is demonstrated by the rapid functionalization of platforms of proven success in supramolecular chemistry and catalysis.

A comprehensively studied class of polydentate amido podands with numerous applications in supramolecular and coordination chemistry is derived from tris(2-aminoethyl)amine (TREN, **1**).[12] Depending on the structural features installed in the tripodal skeleton, TREN-based podands complex either anions or (transition) metal cations, often under participation of the tertiary amine in the coordination process (Figure 1).[8,12]

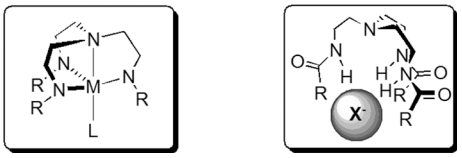
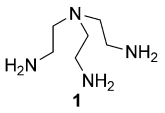
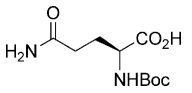
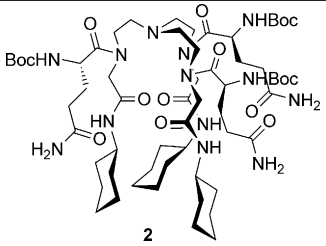
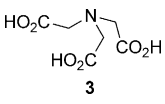
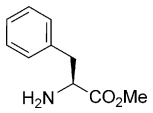
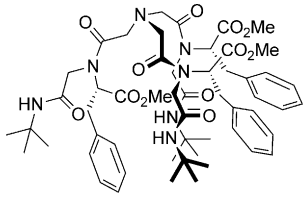
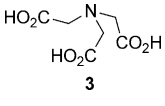
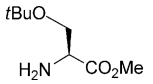
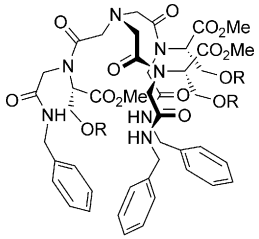
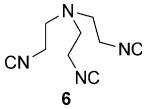
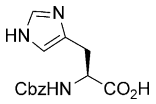
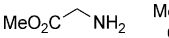
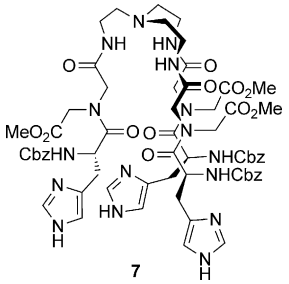
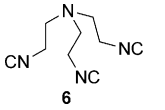
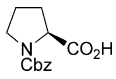
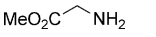
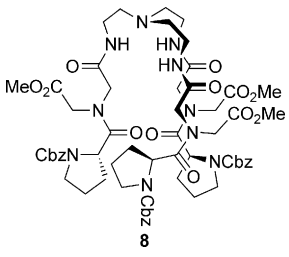


Figure 1. Dual complexation capability of TREN-based podands.

An analogous tripodal skeleton is also available as triacid **3**, and in addition, triamine **1** can be easily converted into triisonitrile **6** through the traditional formylation and dehydration protocols to isonitriles.[8b] Table 1 shows the use of these three tripodal platforms to produce chimeric peptide–peptoid podands by using threefold Ugi-4CRs with monoprotected α-amino acids acting either as the amino or carboxy components. The podands shown incorporate α-amino acids of established recognition or catalytic behavior, that is, glutamine (in **2**), phenyl alanine (in **4**), serine (in **5**), histidine (in **7**), and proline (in **8**). They are but a selection of the more than 25 examples of TREN-based podands produced by parallel multicomponent synthesis for future recognition studies. All proteinogenic α-amino acids can be incorporated into podand architectures in a multifold manner, of which only very few require additional protection[6e,13] for

Table 1. One-pot assembly of chimeric peptide–peptoid podands by threefold Ugi-4CRs of tripodal scaffolds with α-amino acid moieties of recognition and catalytic relevance.[a]

Tripodal core	Appendages		Chimeric podand	Yield [%]
 **1**		$C_6H_{11}NC$	 **2**	56
 **3**		*t*BuNC	 **4**	73
 **3**		BnNC	 TFA ↻ **5a**, R = O*t*Bu; **5b**, R = OH	57[b]
 **6**			 **7**	64
 **6**			 **8**	76

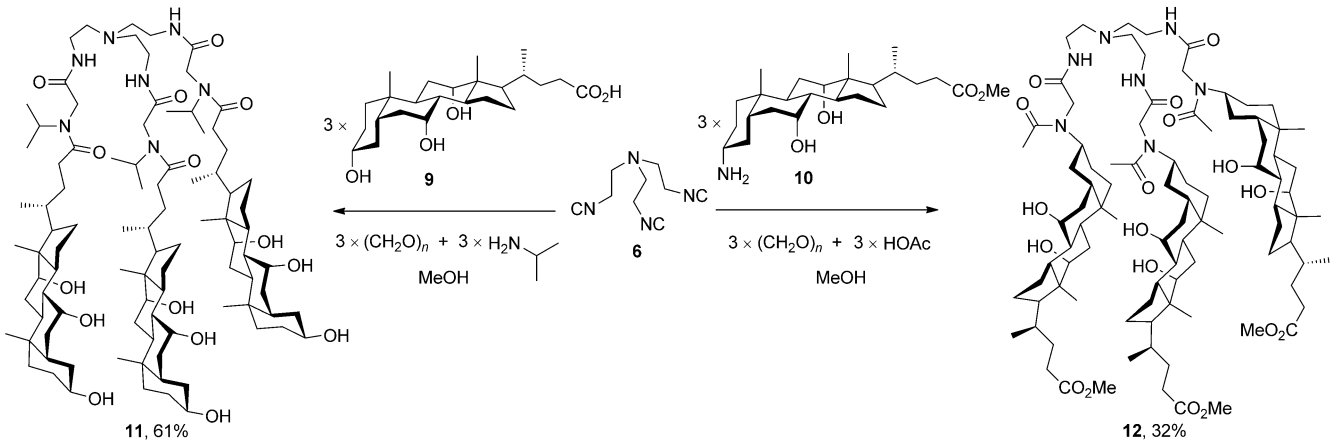
[a] All reactions were conducted in MeOH at room temperature using formaldehyde as the oxo component. [b] Yield over two steps.

side chains known to interfere with the normal course of the Ugi-4CR (i.e., arginine, lysine, aspartic, and glutamic acid).

All chimeric peptide–peptoid podands were obtained in good yields considering the formation of 12 new covalent bonds in a single synthetic operation. Indeed, the procedure can be considered well-suited for the combinatorial synthesis of ligands and receptors as a result of its relatively high chemical efficiency and rapid generation of structural diversity. Triamine **1** afforded the lowest yields among a whole set of center pieces. This might be due to the bulky character of the peptoid moieties branched close to the nitrogen head group, which hampers the completion of the threefold multicomponent process even with small amino acids and isonitriles. Evidence of this was found by following the reaction course by ESI-MS analysis, which shows that the limiting step is not the formation of the third imine moiety but its participation in the third Ugi-4CR once the two initial peptoid chains are formed. As a result, good yields with triamine **1** require much longer reaction times than with triacid **3** or triisonitrile **6**, and even so, still significant amounts (20–25%) of the twofold Ugi-4CR-based products were obtained as byproducts.

It must be noted that peptoid chains, as seen from the head group of the tripodal skeleton, can run either from *N*- to *C*-terminus or vice versa. The use of the three types of trifunctional platforms enables all combinations of threefold Ugi-4CRs to take place, with the consequential increase of podand diversity derived from three different kinds of peptoid branching and directionalities, even with otherwise identical side-chain functionalities (cf., the conceptually identical, detailed discussion of such directional and regioisomerism for macrocycles in ref. [14]). Specificity and directionality of electrostatic interactions such as hydrogen bonding and ion pairing are extremely important in selective supramolecular complex formation. Accordingly, the easy access to counter running peptidic recognition patterns is a key feature for studies of biomimetic binding processes.

In addition to the variations of peptide and peptoid orientation and that provided by canonical amino acids, the scope of this multicomponent approach is boosted by the wide set of other available building blocks that contain Ugi-reactive functional groups. Scheme 2 depicts the synthesis of steroid-armed podands **11** and **12** as examples for the application of non-amino acid building blocks with proven relevance in

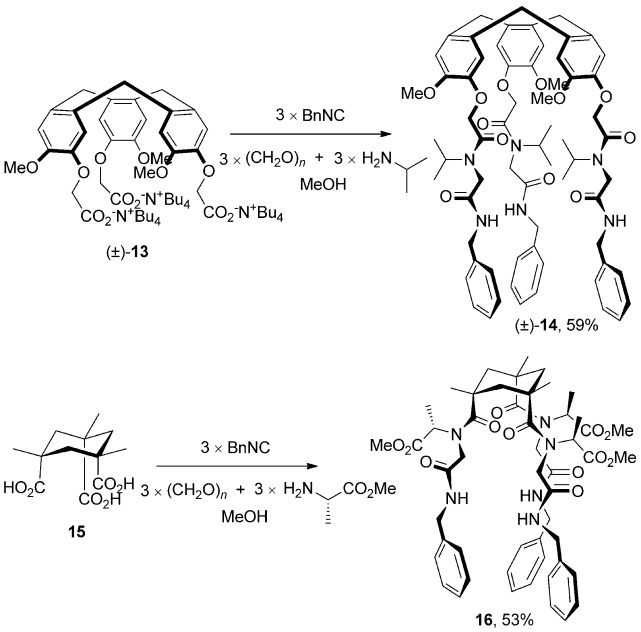


Scheme 2. One-pot assembly of cholane-armed podands by threefold Ugi-4CRs with a tripodal triisonitrile.

recognition studies. They were obtained by employing tripodal triisonitrile **6** and cholanic derivatives presenting carboxylic acid (**9**) and amino (**10**)[15] groups that allow for the Ugi-type multicomponent assembly. Especially the rigid and concave scaffold of bile acids has been widely exploited in supramolecular chemistry[16] and for the construction of steroidal conjugates with biological applications.[17] The incorporation of cholic acid (**9**) into the tripodal podand **11** worked well (61% yield), considering the extremely complex and large structure formed in one step. In contrast, the use of the 3α-cholanyl amine **10** afforded the cholane-armed podand **12** in only 32% yield, showing that the attachment of multiple cholanic arms at the sterically hindered position 3 is more difficult than at the highly flexible side-chain. Interestingly, the final yield of podand **12** could not be improved even after prolonged reaction time (2 days), with the consequent isolation of the corresponding two-armed intermediate in up to 11% yield. The interest to access multicholane-armed architectures in an efficient, straightforward manner is based on their potential as molecular umbrellas, that is, "amphomorphic" compounds that can produce a hydrophobic or hydrophilic exterior when exposed to a hydrophobic or hydrophilic microenvironment.[17a,c] This type of scaffold has been successfully utilized for the transport of biomolecules across membranes and to enhance the bioavailability of drugs.[17a]

Besides the TREN-based tripodal architectures, there are other types of concave, flat and cleft-type platforms with a proven capability for positioning peptide motifs in a preorganized form. Among them are the calixarenes,[18] cyclotriveratrylenes,[19] trialkylbenzenes,[20] Kemp's triacid,[21] and varied steroidal skeletons as asymmetric examples.[16,22] The conformational bias of these scaffolds allows for a specific alignment of binding elements by directing them towards the same side, a feature that has proven to be crucial for mimicking the multivalent character of non-covalent interactions in the biological realm. For example, by functionalizing these scaffolds with suitable peptidic chains, it has been possible to mimic specific types of peptide foldings[21] as well as different kinds of recognition and catalytic profiles of oligopeptides[19,22] and proteins.[20] Accordingly, we envisaged the application of the multiple multicomponent approach to the construction of chimeric peptide–peptoid podands featuring topologically diverse preorganizing platforms.

Scheme 3 exemplifies the use of the bowl-shaped cyclotriveratrylene (CTV)-based triacid **13**[19f,g] and the flat-type Kemp's triacid **15**[21] as templates for the one-pot assembly



Scheme 3. Use of cyclotriveratrylene and Kemp's triacid as templates for the one-pot assembly of aryl-armed, chimeric peptide–peptoid podands by threefold Ugi-4CRs.

of multiple peptide–peptoid hybrid arms bearing aryl groups at the chain tails. To our knowledge, chimeric peptide–peptoid podands based on Kemp's triacid template have been the only type of hybrid peptidic podands produced so far, albeit by traditional peptide-coupling protocols.[21d–f] It must be mentioned that the lower yields of these latter entries are not caused by the topology of the polyfunctional scaffolds but are due to the use of benzylisocyanide, a reagent

that is known to provoke side-reactions derived from its moderate CH-acidity (see also podand **5** in Table 1). In addition to the examples shown, several others were synthesized by varying the nature of the amino and isocyano components, noting that the use of simpler, more nucleophilic isonitriles like cyclohexyl and *tert*-butylisocyanide gave yields over 70% in each case. Nevertheless, the examples highlight the great versatility inherent to MCR-based podand design, because it does not only enable the rapid variation of the chemical nature of the appendages, but also the easy installation of otherwise identical substituents into dissimilar platforms. Since it is well-recognized that the resulting binding profile is not only determined by the presence of the recognition motifs but especially by their appropriate three-dimensional arrangement, the possibility of tuning both elements of diversity in a straightforward, parallel fashion may be seen as the key feature of this methodology towards the combinatorial construction of receptor and ligand libraries.

Despite the C_3-symmetry of these podands, very complex NMR spectra were observed as a result of the occurrence of duplicate signals for the same set of atoms. The detection of several conformers in solution derives from the *cis*/*trans* isomerization of the *N*-substituted amide bonds and is a typical feature of peptoid chemistry. Certainly, the complexity of these structures along with the various combinations of the different *N*-substituted amide configurations makes it impossible to accomplish a detailed interpretation of ^{1}H NMR spectra. Thus, normally, duplicate sets of signals were detected for the amide carbon atoms in ^{13}C NMR spectrum.

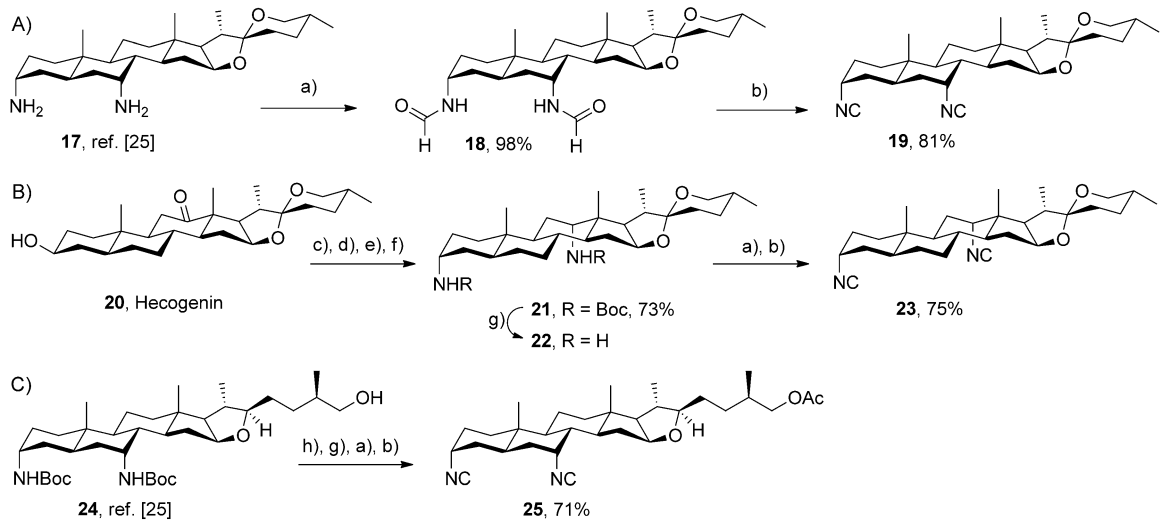
On the other hand, the well-known chemical outcome of the Ugi-4CR along with a precise HR-ESI-MS analysis allows for an unequivocal structural assignment of all chimeric podands. Although the incidence of several conformers arising from the peptide–peptoid hybrid chains complicates the spectroscopic analysis; this may be seen as advantageous in terms of molecular recognition. Firstly, it must be mentioned that the ease of *cis*/*trans*-isomerization does not confer a greater flexibility of peptoid side-chains versus peptide side-chains in general, quite the opposite is often found: peptoids, especially *N*-alkylated peptides not based on polyglycine, commonly have less conformational freedom than peptides because the amide bond rotation is but one element in conformational space.[7] Secondly, the occurrence of various low-energy conformations on the peptoid amide bonds enables to populate a rather different and additional conformational space than the one accessible with normal peptide chains, with the consequence of a higher probability to access a binding conformation not available for peptides.[7] Thirdly, upon the presence of the same type of functionalities, the branched character of the peptoid backbone favors a higher functional density of the recognition elements than those with a linear disposition.[7]

After the grounds of the multiple multicomponent approach to assemble multivalent podands were established, the focus was directed to adopt a rigid center piece in mMCR-chemistry. The one that is most frequently utilized for organizing multilateral functionalities suitable for peptide and anion recognition is the steroid nucleus. Among the different steroidal derivatives available for extensive functionalization, the cholanic skeleton of bile acids has been the most exploited one owing to its high availability and its set of hydroxyl groups properly distributed along the concave platform. Still and co-workers pioneered the use of this scaffold for positioning peptidic chains in a combinatorial fashion, aiming to achieve selective recognition of specific oligopeptides.[22g,h] Meanwhile, the group of Davis has lead the utilization of cholanic derivatives as organizing scaffolds in podand-type anion receptors, namely cholapods.[23] The general approach to achieve effective anion complexing agents has been the replacement of the secondary hydroxyl groups by stronger neutral or positively-charged hydrogen-bond donor groups, such as: urea, thiourea, guanidinium, and sulfonamide.

Along the way to position either hydrogen-bond donors or peptidic chains, a common strategy has been the replacement of the hydroxyls by amino groups.[22,23] Accordingly, we envisaged that aminosteroids could be used (either by themselves or through conversion to the corresponding isocyanosteroids) as platforms for aligning chimeric peptide–peptoid chains. Besides the curved 5β-cholanic scaffolds, it was decided also to employ 5α-steroids with the aim of testing a more extended and flatter polycyclic system. In terms of conformational constrain, the advantage of employing an A/B-*trans* steroidal nucleus containing all functionalities in axial orientation has been well documented.[22g,24] However, this has been only achieved by modifying the *cis* A/B-ring fusion of bile acids.[24] Alternatively, we devised the use of the naturally occurring spirostan and furostan sapogenins, which possess the desired 5α-skeleton and are endowed with functionalization sites on rings A, B, and C.

Scheme 4 shows the synthesis of spirostanic and furostanic diisonitriles from the corresponding amino derivatives.[25] Whereas procedures toward axial aminosteroids are well-established,[26,27] the functionalization of steroids with various axial isocyano groups has not been reported so far. Our approach started with the double formylation of the 3α,7α-diamino-spirostane **17**, previously prepared from the natural sapogenin diosgenin according to a reported procedure.[25] From the different formylation protocols reported for aliphatic amines, the use of ethyl or methyl formate heated at reflux proved ineffective due to the low reactivity of both axial amines, but the mixed formic-acetic anhydride method afforded diformamide **18** in quantitative yield. This compound was submitted to dehydration using the traditional $POCl_3$/Et_3N procedure to furnish 3α,7α-diisocyano-spirostane **19** in 81% yield, thus proving the efficiency of this simple method also on steroids. The relative stereochemistry of both isonitrile groups was confirmed by the narrow shape of the multiplets assigned to the equatorial protons H-3β and H-7β in the ^{1}H NMR spectrum of **19**. As expected, no racemization was detected with this procedure.

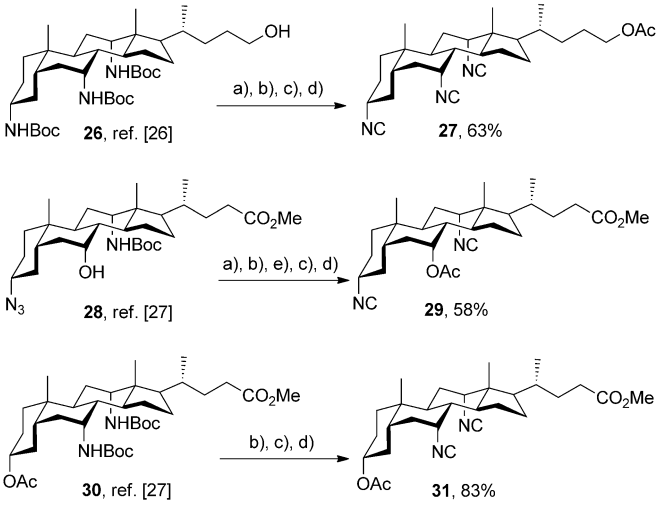
For the preparation of a spirostanic steroid functionalized with isocyano groups on rings A and C, we used a multi-



Scheme 4. Synthesis of A, B) spirostanic diisonitriles and C) furostanic diisonitriles. a) HCO_2H/Ac_2O, then THF, Et_3N; b) $POCl_3$, Et_3N, THF, $-60\rightarrow0\,^{\circ}C$; c) PCC, CH_2Cl_2; d) NH_2OH, AcONa, MeOH, Δ; e) H_2, PtO_2, then Zn, AcOH; f) Boc_2O, THF/aq. sat. $NaHCO_3$; g) TFA, CH_2Cl_2; h) Ac_2O, Py. Abbreviations: Boc = *tert*-butoxycarbonyl; PCC = pyridinium chlorochromate; TFA = trifluoroacetic acid.

step approach previously developed by Davis and co-workers[24,27] to introduce α-oriented amino groups in allocholanes (i.e., A/B-*trans* cholanic substrates). Initially, the natural sapogenin hecogenin (**20**) was submitted to pyridinium chlorochromate (PCC) oxidation to the corresponding diketone, followed by oximation to afford a dioxime intermediate in 94% yield. This compound was subjected to a two-step reduction by using PtO_2-catalyzed hydrogenation followed by treatment with Zn/AcOH to give the corresponding spirostanic 3α,12α-diamine (**22**), which for storage and better handling was then protected as the di-Boc derivative **21** in 73% overall yield. Comparative NMR analysis confirmed the desired α stereochemistry of both amino functions (as carbamates). In our hands, the C-3 epimer of **21** was also obtained as a minor byproduct (6%), whereas the C-12 epimer was not detected. For isonitrile formation, dicarbamate **21** was deprotected with 30% TFA/CH_2Cl_2 and subsequently subjected to the previously standardized formylation and dehydration protocols to furnish the 3α,12α-diisonitrile **23** in 75% yield. Similarly, the furostanic diisonitrile **25** was obtained from furostanol **24** in 71% yield over four steps, that is, protection of the primary hydroxyl group, di-Boc removal, formylation and dehydration exactly as described before.

Scheme 5 shows the synthesis of cholanic polyisonitriles from the corresponding aminocholanes. The cholic acid skeleton is naturally endowed with three functionalization sites, a feature that enables a tunable variation of the position and multiplicity of the Ugi-4CRs through conversion of the hydroxyls into amino and isocyano groups. For example, the tris-Boc cholanic derivative **26** was obtained from methyl cholate according to the multi-step procedure developed by Savage and co-workers,[26] who also confirmed the stereochemistry of the Boc-protected amino groups by X-ray crystallography. The primary hydroxyl of **26** was further protect-



Scheme 5. Synthesis of cholanic tri- and diisonitriles. a) Ac_2O, Py; b) TFA, CH_2Cl_2; c) HCO_2H/Ac_2O, then THF, Et_3N; d) $POCl_3$, Et_3N, THF, $-60\rightarrow0\,^{\circ}C$; e) H_2, 10% Pd/C, EtOH dry.

ed as acetate and the resulting tris-carbamate was submitted sequentially to Boc-removal, formylation and finally to dehydration, without purification of the intermediates, to afford the cholanic triisonitrile **27** in 63% yield over four steps.

In a similar way, the Boc-protected amino-cholanes **28** and **30** were synthesized according to reliable procedures reported by Davis and co-workers,[27] thus providing an array of differentially positioned amino groups for the already standardized conversion to isonitriles. Compound **28**[27b] was initially acetylated and next subjected to Pd-catalyzed hydrogenation to transform the 3α-azido group into an amine. The remaining Boc group was then removed and the resulting diamine was submitted to formylation and subsequent dehydration to afford the cholanic 3α,12α-diisonitrile **29** in

58% yield over four steps. Di-Boc derivative **30**[27a] was equally deprotected, formylated, and dehydrated to furnish the cholanic 7α,12α-diisonitrile **31** in 73% yield.

From the various reports that employ steroids in Ugi-4CRs,[28] we are aware of only two examples that make use of isocyanosteroids[14b,28a] and another two that use aminosteroids.[14b,28d] However, those groups were attached either to the flexible side or to the steroidal nucleus with an equatorial orientation, thereby lacking the reactivity problems usually found in steroid chemistry with axial substituents. But axially-oriented binding elements are preferred in recognition due to the better preorganization induced. Thus, it was important to assess whether sterically hindered, axial amino and isocyano groups are suitable reactants in complex multiple multicomponent reactions. In the initial experiments, steroids having axial isocyano groups afforded excellent results, whereas those with axial amino groups gave only moderate yields, rendering the latter ineffective for the multifold-assembly process. A connected issue is the prospect of a better recognition capability of the peptoid chain derived from the isonitrile-based cores. As illustrated in Figure 2A, the use of aminosteroids furnishes a sterically

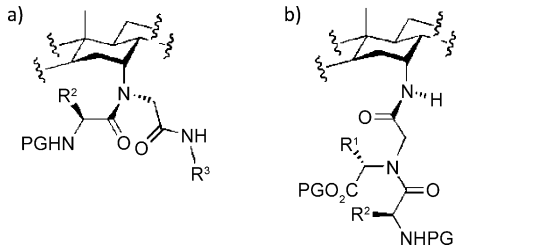


Figure 2. Comparison of the axially oriented, chimeric peptide–peptoid chains resulting from the Ugi-4CR with a) an aminosteroid and b) an isocyanosteroid. The figures represent the position 7α in a putative steroidal skeleton either from the 5α or 5β series. PG = protecting group. R^1 and R^2 = α-amino acid side chains. R^3 = substituent of the isonitrile group.

crowded tertiary amide directly attached close to the bulky steroidal skeleton, with no place for the internal binding of a guest molecule if several such groups are placed on a rigid host surface. In contrast, the use of isocyanosteroids leads to a more convenient peptoid with a C→N directionality running from the steroid at the C-terminus to the N-terminus (Figure 2B). This choice gives rise to a more rigid positioning of the hydrogen-bond donors, as the unsubstituted (peptidic) amides are directly attached to the convergent α-face of the steroidal basis, but at the same time allows more freedom for binding a guest. As a consequence of all this, we suggest isocyanosteroids instead of aminosteroids to produce potential peptidosteroidal receptors by means of multifold Ugi-4CRs.

Table 2 depicts the multicomponent assembly of chimeric peptide–steroids derived from spirostanic-, furostanic-, and cholanic skeletons with mono-protected α-amino acids. Peptido-spirostane **32** was obtained from diisonitrile **19** in 81% by double incorporation of L-alanine methyl ester and *N*-Boc-L-serine, whereas compound **33** was afforded from diisonitrile **23** in 88% yield by including two units of *N*-Cbz-L-proline. Similarly, furostanic diisonitrile **25** was used for the double incorporation of L-alanine methyl ester and *N*-Boc-L-cysteine to furnish peptido-furostane **25** in 73% yield. The high yields achieved in these examples demonstrate the great efficiency of the multicomponent assembly process even by using several axial isocyano groups derived from the *trans* A/B-ring fusion systems. It also proves the feasibility of incorporating multiple organocatalytic (i.e., proline, histidine, and thiols) and binding elements (e.g., hydroxyls, thiol, and carboxylate) in a highly preorganized form caused by the axial positioning of these appendages.

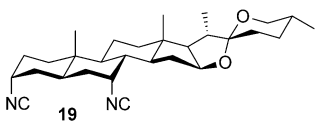
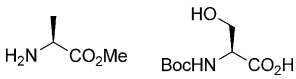
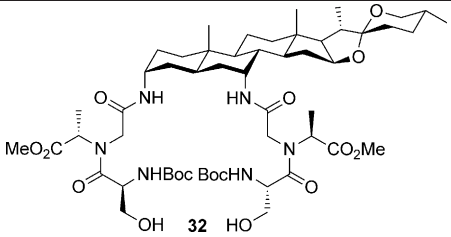
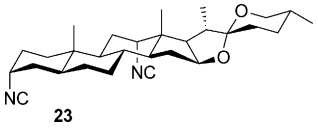
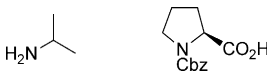
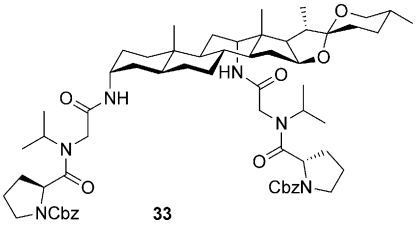
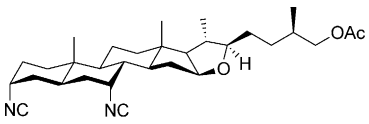
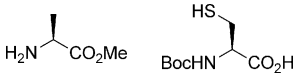
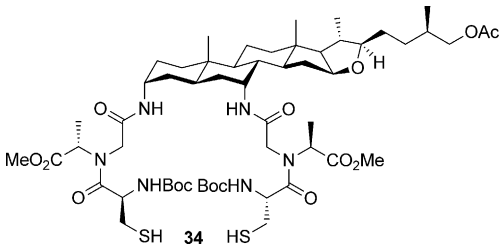
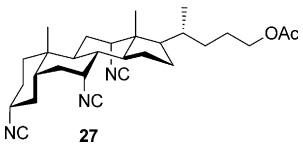
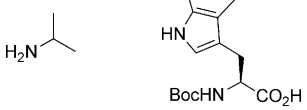
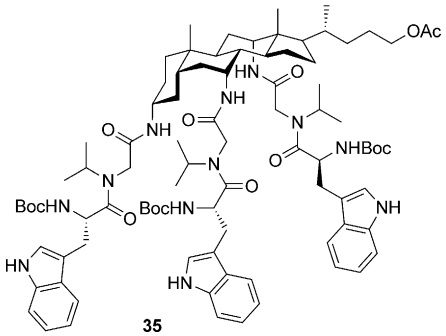
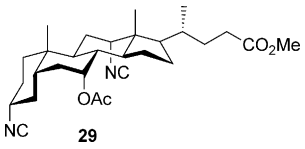
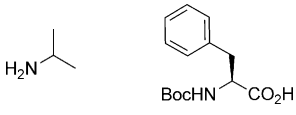
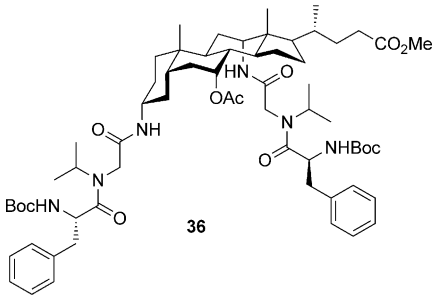
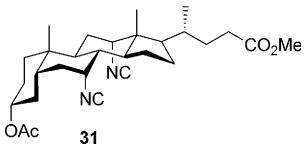
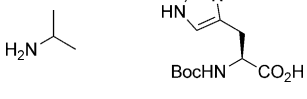
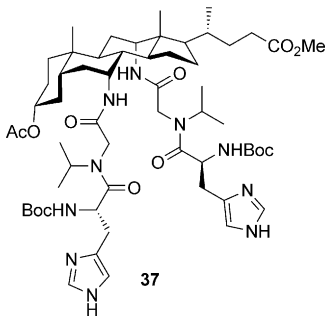
Of special interest is the incorporation of multiple indole, benzyl, and imidazole side-chains. Chimeric peptido-cholanes derived from N^{α}-Boc-protected L-tryptophan, L-histidine, and L-phenylalanine on cholane polyisonitriles **27**, **29**, and **31**, respectively, formed readily, thereby offering a very diverse array of chimeric peptide–peptoid chains attached to a *cis* A/B-steroidal skeleton. Peptido-cholane **35**, obtained in 71% yield, provides a conformationally rigid arrangement of three indole-containing appendages with the potential for organic cation recognition. Similarly, peptido-cholanes **36** and **37** were produced in 82 and 77% yields. Once again, the multiple Ugi-4CRs showed great chemical efficiency with the sterically hindered 7α- and 12α isocyano groups, an important feature for the future combinatorial production of peptido–steroidal receptors. The same strategy is amenable to solid-phase protocols when the carboxylic or hydroxyl functions of the cholanic and furostanic side-chains are attached to a resin bead or another surface, as implemented with great success in solid-phase peptide synthesis.[22,25,29]

Compared with the general methodology used to produce peptido–steroidal receptors through traditional peptide-couplings, the present approach shows greater promise in terms of speed, versatility, atom economy, and binding-motif-generation, especially if sequential approaches are implemented for growing oligochimeric peptide–peptoid chains.[6e,9b,30] We believe that the potential of the Ugi-4CR for complexity generation is now unraveling towards the design of new (pseudo-) peptide-based receptors. This becomes more patent when considering that at least two amino acid units can be incorporated into a rigid, organizing platform in each condensation step, a number that is multiplied by two and three depending on the multifold character of Ugi-4CRs. In addition, our limitation to formaldehyde as oxo-component of the Ugi-4CR is exclusively made for spectroscopic reasons, but with other aldehydes the efficiency is even higher. Also, the utilization of other oxo-components (e.g., amino acid-derived aldehydes, ketones) introduces an additional source of functional diversity (see Scheme 1), thus enhancing the multivalent character of the resulting branched, peptide–peptoid hybrid arms.[9]

Conclusion

The most relevant achievement of the multiple multicomponent assembly process is the possibility to cover a large

Table 2. One-pot assembly of chimeric peptide–steroids by multifold Ugi-4CRs.[a]

Steroidal core	Appendages	Chimeric peptide–steroid	Yield [%]
 **19**		 **32**	81
 **23**		 **33**	88
 **25**		 **34**	73
 **27**		 **35**	71
 **29**		 **36**	82
 **31**		 **37**	77

[a] All reactions were conducted in MeOH at room temperature using formaldehyde as the oxo component.

chemical space of podand arms and topologies in fast one-pot approaches with levels of chemical efficiency suitable for automation. The examples presented herein are but a glimpse of the structural diversity available by the combination of geometrically different organizing platforms (e.g., tripodal, cleft, and concave scaffolds) with the rapid generation of multiple appendages having variable side-chains.[13] Moreover, the number of available podands is not limited to the variation of platforms and functionalized arms, but the N→C directionality and the *endo*/*exo* peptoid combinations discussed previously can further enhance diversity.[9,14] Also, podand arms do not need to be identical and can be assembled by using combinatorial strategies previously applied to macrocycles.[31] Another issue that boosts the versatility of this concept is the plethora of other isonitrile- or even non-isonitrile-based MCRs,[5,32] eventually followed by post-condensation modifications,[33] capable of introducing chemical motifs with potential in recognition and catalytic processes (e.g., nitrogen, sulfur and oxygen-containing heterocycles). Future combinatorial and evolutionary strategies derived from this concept may enhance discovery rates and lead to the emergence of new families of receptors, catalysts, or biologically active ligands based on MCR-motifs.

Experimental Section

General remarks: Melting points were determined on a Leica DM LS2 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer at 399.94 and 100.57 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the TMS (^{1}H NMR) and to the solvent signal (^{13}C NMR). IR spectra were obtained on a Bruker FT-IR spectrometer. High-resolution ESI mass spectra were obtained from a Bruker Apex III Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an Infinity cell, a 7.0 Tesla superconducting magnet, an RF-only hexapole ion guide, and an external electrospray ion source (Agilent, off axis spray). ESI-MS was recorded on a Finnigan TSQ 7000, LC-Tech Ultra Plus pumps, Linear UV/Vis 200 detector, Sepserve Ultrasep ES RP-18 5 μm 1× 100 mm column (flow 70 μL min^{-1}). Flash column chromatography was carried out using Merck silica gel 60 (0.015–0.040 nm) and analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} aluminum sheets. Solid compounds were recrystallized from selected solvents for the melting point measurements. All commercially available chemicals were used without further purification. The syntheses of the isocyanoesteroids **19**, **23**, **25**, **27**, **29**, and **31** are described in the Supporting Information.

General multifold Ugi-4CR-based procedure: The molarities in the following procedure are based on one Ugi-reactive group, see note (2) below. A suspension of the aldehyde (1.0 mmol) and the amine (1.0 mmol) was stirred in MeOH (50 mL) at room temperature until a clear solution was achieved (usually from 1 to 3 h). The carboxylic acid (1.0 mmol) and the isonitrile (1.0 mmol) were subsequently added and the stirring was continued for an additional 12 h. The volatiles were then evaporated under reduced pressure and the resulting crude material was purified by flash column chromatography on silica gel to afford the corresponding podand. Notes: 1) Et_3N ($\leq$1.0 mmol) may be required for the formation of the imine when the amino component is employed as hydrochloride salt (e.g., α-amino acid methyl ester hydrochlorides). 2) The molarities of the polyfunctional building blocks (i.e., triamines, triacids, di- and triisonitriles) have to be adapted to 1/3 or 1/2 of the monofunctional ones, keeping the order of addition of amine and aldehyde, followed by acid and finally isonitrile.

Podand 2: Triamine **1** (0.15 mL, 1.0 mmol), paraformaldehyde (90 mg, 3.0 mmol), *N*-Boc-L-glutamine (738 mg, 3.0 mmol) and cyclohexylisonitrile (0.37 mL, 3.0 mmol) were reacted according to the general threefold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 15:1) afforded podand **2** (698 mg, 56%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$; rotamers and broadened signals are detected): δ=7.68–7.40 (m, 3H, N*H*), 6.56 (br s, 2H, NH_2). 6.48 (br s, 4H, 2×NH_2), 5.33–5.29 (m, 3H, 3×N*H*), 4.57–4.53 (m, 3H, 3×C*H*), 4.31–4.26 (m, 6H, 3×CH_2), 3.92–3.87 (m, 6H, 3×CH_2), 3.76 (m, 3H, 3×C*H*), 3.25–3.20 (m, 6H, 3×CH_2), 2.58–2.54 (m, 6H, 3×CH_2), 1.88 (m, 6H, CH_2-cyclohex.), 1.76–1.64 (m, 12H, CH_2-cyclohex.), 1.48–1.38 (m, 12H, CH_2-cyclohex.), 1.47, 1.46, 1.45 ppm (3 s, 27H, 3×(CH_3)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.0, 174.8, 174.7, 171.9, 171.4, 171.2, 1170.6, 167,8, 167.6, 166.9, 154.9, 80.1, 77.3, 56.6, 53.5, 51.2, 50.8, 40.8, 40.1, 37.7, 28.5, 28.3, 28.1, 24.8, 22.7 ppm; IR (ATR): $\tilde{\nu}$=3335, 3247, 3221, 2967, 2933, 1748, 1672, 1653, 1558, 1540, 1456, 1220 cm^{-1}; HRMS (ESI-FT-ICR): *m/z* calcd for $C_{60}H_{105}NaO_{15}N_{13}$: 1270.7752; found: 1270.7756 [*M*+Na]$^+$.

Podand 4: Triacid **3** (191 mg, 1.0 mmol), paraformaldehyde (90 mg, 3.0 mmol), L-phenylalanine methyl ester hydrochloride (647 mg, 3.0 mmol), Et_3N (0.42 mL, 3.0 mmol), and *tert*-butylisonitrile (0.35 mL, 3.0 mmol) were reacted according to the general threefold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 18:1) afforded podand **4** (740 mg, 73%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$; rotamers and broadened signal are detected): δ=7.31–7.19 (m, 15H, 3×Ph), 4.04 (t, *J*=7.6 Hz, 1H, C*H*), 3.87–3.80 (m, 2H, 2×C*H*), 3.74, 3.75, 3.75 (3 s, 9H, 3×OCH_3), 3.67 (m, 2H, CH_2), 3.55 (m, 2H, CH_2), 3.50 (m, 2H, CH_2), 3.38–3.25 (m, 6H, 3×CH_2), 3.06–3.00 (m, 2H, CH_2), 2.91–2.81 (m, 2H, CH_2), 2.77–2.69 (m, 2H, CH_2), 131.1, 1.30, 1.29 ppm (3 s, 27H, 3×(CH_3)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.5, 170.9, 170.1, 169.8, 166.0, 137.2, 137.1, 129.3, 129.1, 129.0, 128.8, 128.5, 128.2, 126.8, 77.2; 64.7, 64.1, 54.8, 54.0, 52.9, 52.1, 51.6, 51.2, 50.3, 39.8, 34.6, 28.7, 28.6, 28.5 ppm; IR (ATR): $\tilde{\nu}$=3329, 2977, 1742, 1735, 1982, 1667, 1639, 1204, 1167 cm^{-1}; HRMS (ESI-FT-ICR): *m/z* calcd for $C_{54}H_{75}NaO_{12}N_7$: 1036.5370; found: 1036.5372 [*M*+Na]$^+$.

Podand 5: Triacid **3** (191 mg, 1.0 mmol), paraformaldehyde (90 mg, 3.0 mmol), *tert*-butyl L-serine methyl ester hydrochloride (636 mg, 3.0 mmol), Et_3N (0.42 mL, 3.0 mmol), and benzylisocyanide (0.27 mL, 3.0 mmol) were reacted according to the general threefold Ugi-4CR-based procedure. The resulting crude product was dissolved in dry CH_2Cl_2 (10 mL) and treated with trifluoroacetic acid (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. TFA was removed completely by repetitive addition and evaporation of CH_2Cl_2. Flash column chromatography purification (CH_2Cl_2/MeOH 15:1) afforded podand **5** (532 mg, 57%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$; rotamers and broadened signals are detected): δ=8.03 (m, 2H, 2×N*H*), 7.11 (t, *J*=5.4 Hz, 1H, N*H*), 7.31–7.24 (m, 15H, 3×Ph), 5.33 (m, 3H), 5.18 (m, 3H), 4.83 (m, 3H), 4.58 (m, 3H), 4.51–4.39 (m, 6H, 3×CH_2), 4.35–4.20 (m, 6H, 3×CH_2), 4.08–3.97 (m, 6H, 3×CH_2), 3.93–3.70 (m, 6H, 3×CH_2), 3.72, 3.70, 3.68 ppm (3 s, 9H, 3×OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 170.3, 170.1, 169.7, 168.8, 168.7, 137.3, 137.2, 128.6, 127.8, 127.6, 127.5, 61.8, 61.5, 59.6, 59.5, 53.5, 52.7, 52.6, 49.8, 47.7, 43.8, 42.8 ppm; IR (ATR): $\tilde{\nu}$=3352, 3398, 3010, 2968, 1743, 1732, 1678, 1652, 1639, 1108, 1067, 1056, 910 cm^{-1}; HRMS (ESI-FT-ICR): *m/z* calcd for $C_{45}H_{57}NaO_{15}N_7$: 958.3811; found: 958.3819 [*M*+Na]$^+$.

Podand 7: Triisonitrile **6** (176 mg, 1.0 mmol), paraformaldehyde (90 mg, 3.0 mmol), glycine methyl ester hydrochloride (375 mg, 3.0 mmol), Et_3N (0.42 mL, 3.0 mmol), and N^{α}-Cbz-L-histidine (867 mg, 3.0 mmol) were reacted according to the general threefold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH/Et_3N 10:1:0.1) afforded podand **7** (862 mg, 64%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.32 (m, 3H, 3×C*H*-imid.), 7.29 (m, 15H, 3×Ph-Cbz), 6.74 (m, 3H, 3×C*H*-imid.), 5.39 (s, 3H, 3×N*H*), 5.10 (br s, 6H, 3×CH_2), 4.45 (m, 3H, 3×C*H*), 4.25–4.18 (m, 6H, 3×CH_2), 4.02–3.94 (m, 6H, 3×CH_2), 3.87–3.81 (m, 6H, 3×CH_2), 3.75, 3.74 (2 s, 9H, 3×OCH_3), 3.24–3.20 (m, 6H, 3×CH_2), 2.55 ppm (m, 6H, 3×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.1, 169.7, 169.6, 168.5, 156.2, 139.2, 136.3, 135.7, 128.4, 127.9, 127.8,

117.0, 116.9, 70.2, 66.8, 54.2, 51.8, 49.6, 52.4, 43.4, 37.5 ppm; IR (ATR): $\tilde{\nu}$ = 3064, 2955, 1734, 1731, 1694, 1683, 1665, 1206, 1202, 1158 cm^{-1}; HRMS (ESI-FT-ICR): *m/z* calcd for $C_{63}H_{78}NaN_{16}O_{18}$: 1369.5579; found: 1369.5574 $[M+Na]^+$.

Podand 8: Triisonitrile **6** (176 mg, 1.0 mmol), paraformaldehyde (90 mg, 3.0 mmol), glycine methyl ester hydrochloride (375 mg, 3.0 mmol), Et_3N (0.42 mL, 3.0 mmol), and *N*-Cbz-L-proline (747 mg, 3.0 mmol) were reacted according to the general threefold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 12:1) afforded podand **8** (931 mg, 76%) as a pale brown oil. ^{1}H NMR (400 MHz, $CDCl_3$; rotamers and broadened signals are detected): δ = 7.37–7.30 (m, 15H, 3×Ph-Cbz), 5.13–5.00 (m, 6H, 3×CH_2), 4.74–4.46 (m, 3H, 3×C*H*), 4.21–4.09 (m, 6H, 3×CH_2), 3.78, 3.77, 3.75 (3 s, 9H, 3×OCH_3), 3.63–3.49 (m, 12H, 6×CH_2), 3.32–3.24 (m, 6H, 3×CH_2), 2.53 (m, 6H, 3×CH_2), 2.28–2.12 (m, 6H, 3×CH_2), 2.00–1.91 ppm (m, 6H, 3×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 170.8, 170.4, 168.5, 154.9, 136.5, 128.4, 127.9, 127.7, 127.5, 66.9, 56.5, 53.0, 52.5, 50.6, 46.8, 45.5, 38.2, 29.8, 24.0 ppm; IR (ATR): $\tilde{\nu}$ = 3317, 3064, 2953, 1697, 1693, 1635, 1467, 1248, 1211, 1168 cm^{-1}; HRMS (ESI-FT-ICR): *m/z* calcd for $C_{60}H_{78}NaO_{18}N_{10}$: 1249.5396; found: 1249.5395 $[M+Na]^+$.

Podand 11: Triisonitrile **6** (88 mg, 0.5 mmol), paraformaldehyde (45 mg, 1.5 mmol), isopropylamine (0.13 mL, 1.5 mmol), and cholic acid **9** (610 mg, 1.5 mmol) were reacted according to the general threefold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 5:1) afforded podand **11** (492 mg, 61%) as a white solid. M.p. (from MeOH): 263–266 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 4.26–4.22 (m, 3H), 4.12–4.06 (m, 6H, 3×CH_2), 3.96 (m, 3H, 3×C*H*), 3.79 (m, 3H, 3×C*H*), 3.36 (m, 3H, 3×C*H*), 3.25–3.20 (m, 6H, 3×CH_2), 1.28–1.22 (m, 18H, 3×(CH_3)$_2$CH), 1.00 (s, 9H, 3×CH_3), 0.91 (m, 9H, 3×CH_3), 0.71 ppm (m, 9H, 3×CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ = 170.2, 169.8, 169.4, 71.8, 69.1, 68.7, 56.4, 52.3, 51.4, 48.9, 47.8, 44.6, 42.7, 42.0, 40.3, 40.1, 39.8, 36.4, 35.8, 35.3, 34.5, 33.0, 31.3, 30.5, 28.7, 27.1, 26.3, 24.1, 23.3, 20.7, 18.6, 12.1 ppm; IR (KBr): $\tilde{\nu}$ = 3420, 3365, 2935, 2868, 1684, 1667, 1656, 1622, 1463, 1444, 1251, 1193, 1073, 1044 cm^{-1}; HRMS (ESI-FT-ICR): *m/z* calcd for $C_{93}H_{159}O_{15}N_7$: 1614.1801; found: 1614.1786 $[M+H]^+$.

Podand 12: Triisonitrile **6** (88 mg, 0.5 mmol), paraformaldehyde (45 mg, 1.5 mmol), cholanyl amine **10** (635 mg, 1.5 mmol) and acetic acid (0.09 mL, 1.5 mmol) were reacted according to the general threefold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 5:1) afforded podand **12** (263 mg, 32%) as a white solid. M.p. (from MeOH): 298–301 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 4.02–3.98 (m, 6H, 3×CH_2), 3.92 (m, 3H, 3×C*H*), 3.83 (m, 3H, 3×C*H*), 3.59 (s, 9H, 3×CH_3O), 3.51 (m, 3H, 3×C*H*), 3.31–3.24 (m, 6H, 3×CH_2), 2.08 (s, 9H, 3×CH_3), 0.97 (s, 9H, 3×CH_3), 0.92 (m, 9H, 3×CH_3), 0.68 ppm (s, 9H, 3×CH_3). ^{13}C NMR (100 MHz, CD_3OD): δ = 174.3, 169.8, 169.1, 70.2, 69.4, 67.3, 54.7, 52.8, 50.2, 47.6, 47.0, 45.2, 44.5, 42.4, 42.2, 40.8, 39.6, 36.2, 35.7, 35.5, 34.5, 33.2, 31.0, 30.7, 26.8, 24.0, 23.1, 21.8, 19.6, 18.2, 12.6 ppm; IR (KBr): $\tilde{\nu}$ = 3377, 3355, 2939, 2892, 1741, 1734, 1732, 1692, 1671, 1654, 1454, 1432, 1248, 1073, 1065, 1044 cm^{-1}; HRMS (ESI-FT-ICR): *m/z*: calcd for $C_{92}H_{151}O_{18}N_7$: 1642.1114; found: 1642.1116 $[M+H]^+$.

Podand 14: CTV-based triacid **13** (653 mg, 0.5 mmol, dissolved in 10 mL of H_2O), paraformaldehyde (45 mg, 1.5 mmol), isopropylamine (0.13 mL, 1.5 mmol) and benzylisocyanide (0.14 mL, 1.5 mmol) were reacted according to the general threefold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 15:1) afforded podand **14** (338 mg, 59%) as a white solid. M.p. (from EtOAc): 221–223 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (m, 15H, 3×Ph), 6.82 (m, 3H, Ar), 6.75 (m, 3H, Ar), 4.70 (m, 3H), 4.64 (m, 6H, 3×CH_2), 4.57–4.50 (m, 6H, 3×CH_2), 4.26–4.21 (m, 6H, 3×CH_2), 4.15–4.09 (m, 3H, 3×C*H*), 3.80 (s, 9H, 3×OCH_3), 3.72 (s, 9H, 3×OCH_3), 3.59 (m, 3H), 1.07–1.01 ppm (m, 18H, 3×(CH_3)$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 169.0, 148.0, 145.4, 138.0, 133.8, 131.2, 128.1, 127.3, 127.0, 126.8, 116.4, 113.5, 69.0, 58.4, 55.7, 48.7, 42.6, 36.0, 30.7, 23.5, 20.7, 19.4, 13.4 ppm; HRMS (ESI-FT-ICR): *m/z* calcd for $C_{66}H_{78}NaO_{12}N_6$: 1169.5569; found: 1169.5556 $[M+Na]^+$.

Podand 16: Kemp's triacid **15** (129 mg, 0.5 mmol), paraformaldehyde (45 mg, 1.5 mmol), (0.13 mL, 3.0 mmol) and benzylisocyanide (0.14 mL, 1.5 mmol) were reacted according to the general threefold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 15:1) afforded podand **16** (253 mg, 53%) as a white solid. M.p. (from MeOH): 170–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (m, 15H, 3×Ph), 7.69 (m, 3H, 3×N*H*), 4.54–4.47 (m, 3H, 3×C*H*), 3.95–3.92 (m, 6H, 3×CH_2), 3.76, 3.74, 3.73 (3 s, 9H, 3×CH_3O), 3.41–3.37 (m, 6H, 3×CH_2), 2.45 (d, *J* = 12.6 Hz, 3H, CH_2), 2.37 (d, *J* = 14.0 Hz, 3H, CH_2), 1.19 (s, 9H, 3×CH_3), 1.08–0.99 ppm (m, 6H, 3×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 170.4, 170.1, 169.8, 138.2, 125.7, 124.9, 122.9, 51.5, 51.3, 48.1, 44.2, 42.3, 30.8, 21.3 ppm; HRMS (ESI-FT-ICR): *m/z* calcd for $C_{51}H_{66}NaO_{12}N_6$: 977.4637; found: 977.442 $[M+Na]^+$.

Spirostanic peptide–peptoid hybrid 32: Diisocyanide **19** (225 mg, 0.5 mmol), paraformaldehyde (30 mg, 1.0 mmol), *N*-Boc-L-serine (205 mg, 1.0 mmol), L-alanine methyl ester hydrochloride (139 mg, 1.0 mmol), and Et_3N (0.14 mL, 1.0 mmol) were reacted according to the general polyfold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 12:1) afforded **32** (417 mg, 81%) as a white solid. M.p. (from MeOH): 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.01 (m, 1H, N*H*), 5.82 (m, 1H, N*H*), 4.80–4.72 (m, 2H, C*H*), 4.67 (dd, *J* = 8.6/4.2 Hz, 1H, C*H*), 4.62 (dd, *J* = 8.7/4.4 Hz, 1H, C*H*), 4.43 (m, 1H, C*H*), 4.32–4.25 (m, 4H, 2×CH_2), 3.92–3.88 (m, 4H, 2×CH_2), 3.81 (m, 1H, C*H*), 3.72 (m, 1H, C*H*), 3.68 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.45 (m, 1H, C*H*), 3.34 (t, *J* = 10.9 Hz, 1H, C*H*), 1.43 (s, 9H, (CH_3)$_2$C), 1.42 (s, 9H, (CH_3)$_2$C), 0.97 (d, *J* = 6.4 Hz, 3H, H-21), 0.92 (s, 3H, H-19), 0.83 (s, 3H, H-18), 0.79 ppm (d, 3H, *J* = 6.3 Hz, H-27); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 174.0, 170.5, 170.2, 170.1, 169.7, 168.8, 168.7, 154.9, 154.6, 109.4, 80.9, 80.4, 80.2, 71.4, 70.8, 66.6, 62.2, 61.8, 61.6, 59.4, 59.3, 56.0, 54.4, 53.6, 53.5, 52.7, 52.6, 49.8, 47.7, 47.6, 43.8, 42.8, 41.7, 40.7, 40.1, 39.6, 38.6, 35.6, 35.0, 31.7, 31.4, 31.2, 30.1, 30.0, 28.8, 28.5, 28.3, 28.1, 19.2, 17.1, 16.7, 14.5, 13.8 ppm; IR (KBr): $\tilde{\nu}$ = 3446, 3381, 2930, 2871, 1998, 1677, 1664, 1651, 1455, 1366, 1240, 1170, 1053, 979, 919, 899, 865 cm^{-1}; HRMS (ESI-FT-ICR): *m/z* calcd for $C_{55}H_{90}NaN_6O_4$: 1113.6317; found: 1113.6324 $[M+Na]^+$.

Spirostanic peptide–peptoid hybrid 33: Diisocyanide **23** (225 mg, 0.5 mmol), paraformaldehyde (30 mg, 1.0 mmol), isopropylamine (0.09 mL, 1.0 mmol), and *N*-Cbz-L-proline (249 mg, 1.0 mmol) were reacted according to the general polyfold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 18:1) afforded **33** (480 mg, 88%) as a white solid. M.p. (from MeOH): 147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 10H, 2×Ph), 5.86 (m, 1H, N*H*), 5.68 (m, 1H, N*H*), 5.23–5.17 (m, 2H, CH_2), 5.03–4.95 (m, 2H, CH_2), 4.78–4.74 (m, 1H, C*H*), 4.71–4.66 (m, 1H, C*H*), 4.59 (m, 1H, C*H*), 4.54 (m, 1H, C*H*), 4.34 (m, 1H, C*H*), 4.30–4.19 (m, 2H, CH_2), 4.04–3.98 (m, 2H, CH_2), 3.90 (m, 1H, C*H*), 3.79–3.68 (m, 3H), 3.65–3.55 (m, 2H), 3.43 (m, 1H, C*H*), 3.32 (t, *J* = 10.6 Hz, 1H, C*H*), 1.25 (d, 6H, *J* = 6.4 Hz, (CH_3)$_2$CH), 1.15 (d, *J* = 6.4 Hz, 6H, (CH_3)$_2$CH), 0.94 (d, *J* = 6.7 Hz, 3H, H-21), 0.81 (s, 3H, H-19), 0.77 (d, *J* = 6.2 Hz, 3H, H-27), 0.68 ppm (s, 3H, H-18); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 172.6, 169.4, 168.6, 154.7, 154.6, 136.5, 136.4, 128.4, 128.3, 127.9, 127.8, 127.6, 127.4, 109.3, 80.4, 77.2, 66.9, 66.7, 59.9, 57.1, 56.9, 56.8, 56.6, 55.6, 53.4, 49.0, 48.8, 46.7, 45.8, 45.4, 45.1, 42.3, 40.7, 36.2, 36.1, 33.9, 33.0, 32.3, 31.9, 31.8, 31.4, 30.2, 30.0, 29.9, 28.9, 28.3, 27.4, 25.5, 24.9, 24.7, 22.7, 21.1, 20.8, 19.7, 17.2, 13.5, 11.9, 11.3 ppm; IR (KBr): $\tilde{\nu}$ = 3446, 3063, 2928, 2874, 1705, 1692, 1664, 1658, 1459, 1425, 1179, 981, 899, 765 cm^{-1}. HRMS (ESI-FT-ICR): *m/z* calcd for $C_{63}H_{91}N_6O_{10}$: 1191.6794; found: 1191.6799 $[M+H]^+$.

Furostanic peptide–peptoid hybrid 34: Diisocyanide **25** (247 mg, 0.5 mmol), paraformaldehyde (30 mg, 1.0 mmol), *N*-Boc-L-cysteine (221 mg, 1.0 mmol), L-alanine methyl ester hydrochloride (139 mg, 1.0 mmol) and Et_3N (0.14 mL, 1.0 mmol) were reacted according to the general polyfold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 15:1) afforded **34** (426 mg, 73%) as a white solid. M.p. (from EtOAc): 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 2H, 2×N*H*), 5.29 (m, 2H, 2×N*H*), 4.58–4.53 (m, 2H, 2×C*H*), 4.33–4.28 (m, 3H), 4.24–4.19 (m, 4H, 2×CH_2), 3.97–3.90 (m, 2H), 3.82 (m, 1H, C*H*), 3.73 (m, 1H, C*H*), 3.76, 3.73 (2 s, 6H, 2×CH_3O), 3.52–3.44 (m, 2H, C*H*), 3.32 (m, 1H, C*H*), 2.82–2.77 (m, 4H, 2×CH_2), 2.02 (s, 1H, CH_3CO), 1.61–1.55 (m, 2H), 1.47 (d, *J* = 7.2 Hz, 3H, CH_3), 1.45 (d, *J* = 7.2 Hz, 3H, CH_3), 1.42, 1.40 (2 s, 18H, 2×(CH_3)$_3$C),

0.98 (d, J=6.6 Hz, 3H, CH_3), 0.91 (d, J=6.5 Hz, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.80 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.0, 171.4, 171.2, 170.4, 167.8, 167.5, 154.9, 154.8, 90.4, 80.0, 79.9, 83.3, 78.9, 78.8, 69.9, 56.5, 56.7, 56.0, 54.5, 52.6, 52.5, 52.3, 52.0, 51.5, 51.3, 51.0, 50.9, 50.0, 47.9, 46.8, 42.2, 39.4, 39.1, 38.1, 37.0, 35.7, 32.2, 32.0, 31.5, 30.4, 30.2, 28.6, 28.5, 28.45, 28.4, 28.3, 21.3, 20.6, 18.8, 18.3, 16.5, 16.4 ppm; IR (KBr): $\tilde{\nu}$=3437, 3389, 2939, 2865, 1724, 1685, 1676, 1669, 1654, 1457, 1369, 1034 cm^{-1}; HRMS (ESI-FT-ICR): m/z calcd for $C_{57}H_{94}N_6NaO_{15}S_2$: 1189.6120; found: 1189.6116 $[M+Na]^+$.

Cholanic peptide–peptoid hybrid 35: Trisocyanide **27** (232 mg, 0.5 mmol), paraformaldehyde (45 mg, 1.5 mmol), isopropylamine (0.13 mL, 1.5 mmol), and N^{α}-Boc-L-tryptophan (456 mg, 1.5 mmol) were reacted according to the general threefold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 20:1) afforded **35** (564 mg, 71%) as a white solid. M.p. (from EtOAc): 194–196°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.27 (m, 1H, NH), 8.15 (m, 1H, NH), 7.67 (m, 1H, NH), 7.36–7.09 (m, 15H, 3×Ph), 6.97 (m, 1H, NH), 6.94 (m, 1H, NH), 6.91 (m, 1H, NH), 5.34 (m, 1H, NH), 5.24 (m, 1H, NH), 5.07 (m, 1H, NH), 4.45–3.02 (m, 23H), 2.02 (s, 3H, CH_3CO), 1.46, 1.44, 1.42 (3 s, 27H, (CH_3)$_3$C), 1.37–1.32 (m, 12H, 2×(CH_3)$_2$CH), 1.25 (m, 6H, (CH_3)$_2$CH), 0.99 (s, 3H, H-19), 0.83 (s, 3H, H-18), 0.82 ppm (d, J= 6.2 Hz, 3H, H-21); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.9, 173.6, 173.3, 171.5, 169.3, 168.9, 168.6, 168.4, 155.2, 155.1, 155.0, 136.2, 136.0, 127.4, 127.2, 127.0, 123.6, 124.4, 123.0, 122.1, 121.9, 121.6, 119.7, 119.4, 118.4, 117.7, 11.3, 110.3, 110.0, 80.7, 80.3, 80.0, 64.9, 53.4, 52.0, 50.7, 50.4, 40.0, 49.5, 49.3, 48.9, 48.7, 46.6, 46.4, 46.3, 45.9, 45.2, 44.3, 44.1, 37.0, 36.7, 36.5, 35.3, 35.0, 32.1, 31.9, 31.1, 30.5, 30.0, 29.6, 29.2, 28.6, 28.4, 28.3, 28.2, 28.0, 27.6, 27.4, 26.3, 25.7, 25.6, 24.6, 23.5, 23.4, 22.7, 21.7, 21.5, 21.0, 20.7, 20.3, 19.7, 19.4, 17.7, 14.1, 13.2 ppm; IR (KBr): $\tilde{\nu}$=3427, 3092, 3031, 2970, 1724, 1669, 1654, 1543, 1451, 1229, 1172, 1031 cm^{-1}; HRMS (ESI-FT-ICR): m/z calcd for $C_{89}H_{128}NaN_{12}O_{14}$: 1611.9550; found: 1611.9539 $[M+Na]^+$.

Cholanic peptide–peptoid hybrid 36: Diisocyanide **29** (241 mg, 0.5 mmol), paraformaldehyde (30 mg, 1.0 mmol), isopropylamine (0.09 mL, 1.0 mmol), and N-Boc-L-phenylalanine (275 mg, 1.0 mmol) were reacted according to the general polyfold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 20:1) afforded **36** (474 mg, 82%) as a white solid. M.p. (from CH_2Cl_2/n-hexane): 134–136°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.29–7.18 (m, 10H, 2×Ph), 6.97 (m, 1H, NH), 6.37 (m, 1H, NH), 6.08 (m, 1H, NH), 5.86 (m, 1H, NH), 4.99 (m, 1H, CH), 4.40–4.34 (m, 2H), 4.27–4.15 (m, 4H), 3.81–3.79 (m, 2H), 3.73 (m, 1H, CH), 3.65 (s, 3H, OCH_3), 3.59 (m, 1H, CH), 2.01 (s, 3H, CH_3CO), 1.40 (s, 9H, (CH_3)$_3$C), 1.37 (s, 9H, (CH_3)$_3$C), 1.26–1.22 (m, 12H, (CH_3)$_2$CH), 0.96 (s, 3H, H-19), 0.85 (d, 3H, J=5.6 Hz, H-21), 0.80 ppm (s, 3H, H-18); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.3, 173.2, 172.7, 172.6, 171.0, 170.4, 169.0, 168.8, 168.2, 155.0, 154.8, 136.5, 136.3, 136.1, 135.7, 129.1, 128.5, 128.4, 127.0, 126.8, 80.4, 80.0, 76.2, 74.6, 71.3, 70.8, 60.4, 51.8, 51.5, 51.2, 49.5, 49.3, 48.5, 48.3, 46.3, 45.9, 45.8, 44.7, 44.5, 44.3, 41.4, 40.9, 40.0, 39.6, 36.9, 35.3, 35.0, 34.8, 34.6, 31.8, 31.4, 31.0, 30.6, 28.5, 28.4, 28.3, 27.5, 26.9, 26.3, 23.3, 23.0, 22.7, 21.7, 21.6, 20.7, 20.3, 17.2, 14.3, 13.5 ppm; IR (KBr): $\tilde{\nu}$=3433, 3085, 3026, 2972, 2937, 1735, 1712, 1680, 1521, 1453, 1367, 1247, 1170, 1027 cm^{-1}; HRMS (ESI-FT-ICR): m/z calcd for $C_{65}H_{98}NaN_6O_{12}$: 1177.7135; found: 1177.7150 $[M+Na]^+$.

Cholanic peptide–peptoid hybrid 37: Diisocyanide **31** (241 mg, 0.5 mmol), paraformaldehyde (30 mg, 1.0 mmol), isopropylamine (0.09 mL, 1.0 mmol), and N-Cbz-L-histidine (289 mg, 1.0 mmol) were reacted according to the general polyfold Ugi-4CR-based procedure. Flash column chromatography purification (CH_2Cl_2/MeOH 15:1) afforded **37** (463 mg, 77%) as a white solid. M.p. (from EtOAc): 139–140°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.47 (m, 2H, 2×CH-imid.), 7.31 (m, 5H, Ph), 7.29 (m, 5H, Ph), 6.74 (m, 2H, 2×CH-imid.), 5.89 (m, 1H, NH), 5.08 (m, 2H, CH_2), 5.04 (s, 2H, CH_2), 4.87–4.84 (m, 2H), 4.54 (br m, 1H, CH), 4.23–4.19 (m, 2H, CH_2), 4.15–4.10 (m, 2H, CH_2), 3.84 (m, 1H, CH), 3.62 (m, 1H, CH), 3.59 (s, 3H, OCH_3), 1.18 (d, J=6.6 Hz, 6H, (CH_3)$_2$CH), 1.14 (d, J=6.6 Hz, 6H, (CH_3)$_2$CH), 0.97 (s, 3H, H-19), 0.81 (d, J=6.0 Hz, 3H, H-21), 0.78 ppm (s, 3H, H-18); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.4, 170.4, 172.6, 171.7, 170.4, 169.0, 155.5, 155.4, 136.0, 135.7, 128.4, 128.0, 127.8, 77.2, 74.4, 67.0, 66.8, 51.5, 50.9, 49.4, 49.0, 48.4, 46.4, 44.6, 44.3, 43.9, 41.1, 36.9, 35.2, 35.0, 34.9, 32.1, 31.3, 30.8, 29.5, 28.6, 27.3, 26.4, 25.6, 23.3, 22.8, 21.8, 21.8, 21.7, 21.5, 20.4, 20.3, 17.2, 13.2 ppm; IR (KBr) $\tilde{\nu}$= 3411, 3065, 3033, 2939, 2871, 1727, 1655, 1583, 1451, 1247, 1050, 1027 cm^{-1}; HRMS (ESI-FT-ICR): m/z calcd for $C_{65}H_{91}N_{10}O_{12}$: 1203.6812; found: 1202.6812 $[M+H]^+$.

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