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Design, Synthesis, and Conformational Analysis of Trispyrimidonamides as α-Helix Mimetics

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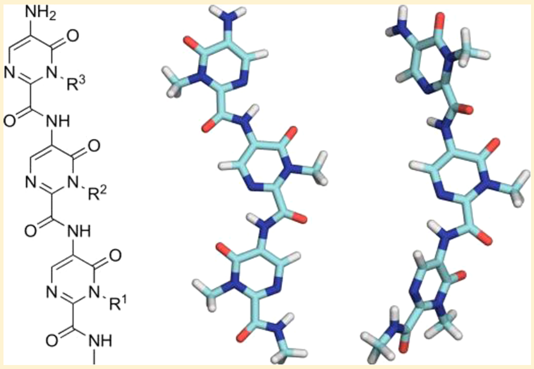
S *Supporting Information*

ABSTRACT: The straightforward synthesis of trispyrimidonamides as a new class of α-helix mimetics is reported. Because of the versatility of our synthetic protocol, a variety of side chains including aliphatic, basic, aromatic, and heteroaromatic residues were included. A comprehensive conformational analysis revealed that in polar solvents a trimeric compound adopts conformations that can lead to i, i + 4, i + 8, or i, i + 8 patterns of side chain orientation. This suggests that trispyrimidonamides could be promising α-helix mimetics to target hot spots that are distributed over a wider angular range of an α-helix interface than in the classical i, i + 4, i + 7 case.

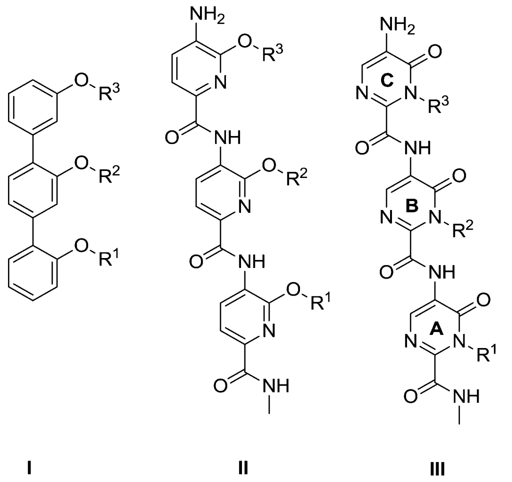


INTRODUCTION

Protein−protein interactions (PPIs) are involved in the regulation of numerous essential cellular processes[1−7] and play a central role in disease development.[8−10] Consequently, modulating PPIs is a promising concept to interfere with physiological and pathophysiological processes.[1,7,11−13] Small molecule protein−protein interaction modulators (PPIMs) that efficiently and selectively affect protein−protein binding are one way of interference.[14−18] The most frequently occurring recognition motifs in PPIs are α-helices.[19,20] This and the fact that usually only a few key residues (so-called "hot spots") in a protein−protein interface account for the majority of the binding affinity[21−23] have fueled the development of small molecules mimicking α-helices (Scheme 1).[24−32]

Such small-molecule α-helix mimetics have proven valuable as biophysical probes or modulators of protein−protein interactions.[10,27,33] Compared to other α-helix mimetics, e.g., β-peptides, aza- and aminoxypeptides, γ-peptides, and peptoids, small-molecule α-helix mimetics promise to have more favorable pharmacokinetic properties.[34] The development of small-molecule α-helix mimetics started almost 30 years ago with the synthesis of 1,6-disubstituted indanes where the substituents mimic the i and i + 1 residues of an α-helix.[35,36] A pioneering advancement was the synthesis of tris-ortho-substituted terphenyl derivatives by Hamilton and co-workers;[37] the substituents of this extended scaffold mimic the i, i + 4, and i + 7 residues of an α-helix. In search for small-molecule α-helix mimetics that have more hydrophilic and/or amphiphilic scaffolds than the terphenyls, terpyridines, trisbenzamides, terephthalamides, trispyridylamides, phenylenaminones, pyridazine, 1,4-benzodiazine-2,5-diones, trisubstituted imidazoles, benzylidenechalcones, and trans-fused poly-

Scheme 1. (I) Terphenyl, (II) Trispyridylamide, and (III) Trispyrimidonamide[a]



[a]Scaffold rings of **III** are labeled A, B, C.

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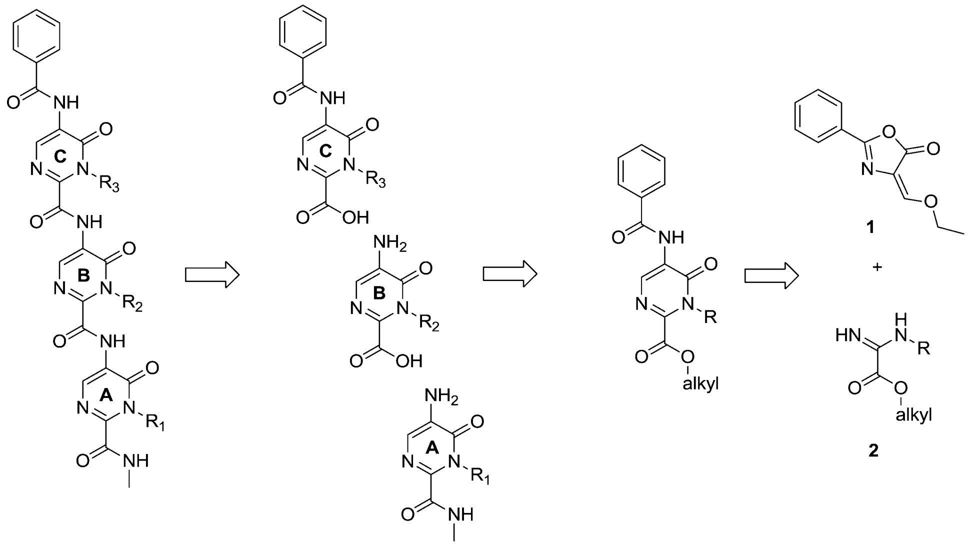
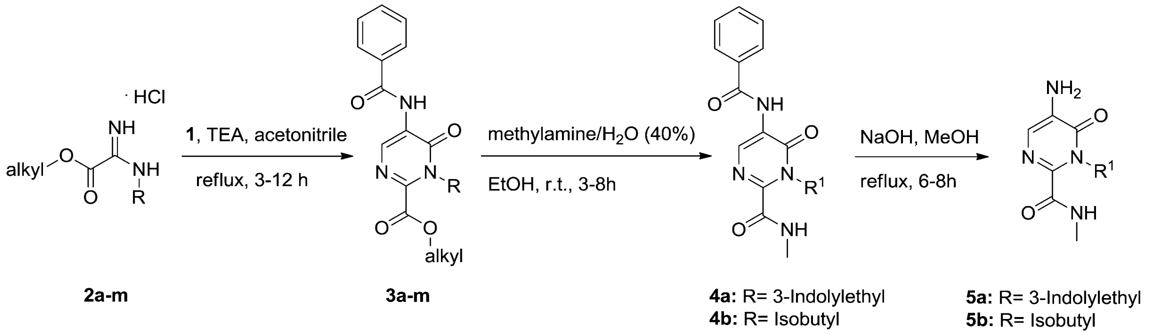
Scheme 2. Retrosynthesis of the Trispyrimidonamide Scaffold



Scheme 3. Synthesis of Monomers 3 and 5-Aminopyrimidones 5a,b



cyclic ethers were synthesized.[38−49] For several of these scaffolds, only *n*-alkyl, *i*-alkyl, or arylalkyl substituents have been reported[43,48−50] likely because of synthetic difficulties when introducing polar and/or charged substituents. As a consequence, only hydrophobic or aromatic side chains of hot spots can be mimicked. This may lead to a restricted applicability if the frequently occurring hot spots Trp, Tyr, and Arg are to be addressed.[51,52]

This provided the incentive for us to design and synthesize previously unreported trispyrimidonamides as a new class of α-helix mimetics and investigate by 2D NMR, X-ray crystallography, and molecular modeling their conformational properties. Regarding the synthesis, our approach provides a general toolbox that allows generating trispyrimidonamides with hydrophobic and differently functionalized (aliphatic, aromatic, heteroaromatic, polar, and basic) side chains. That way, a variety of potential hot spots can be mimicked by the R-groups of our trispyrimidonamide scaffold. The 2D NMR experiments together with modeling studies suggest that trispyrimidonamide derivatives adopt conformations in polar solvents that can orient R groups in such a way that they mimic amino acid side chains at positions *i*, *i* + 4, *i* + 8 or *i*, *i* + 8 of an α-helix. The *i*, *i* + 4, *i* + 8 pattern is currently targeted by just one class of mimetics.[53]

■ RESULTS AND DISCUSSION

Chemistry. We decided to pursue a monomer approach in order to develop a synthetic protocol that allows a high structural diversity for our desired trimeric α-helix mimetics. The synthesis of polysubstituted pyrimidines is usually accomplished by (i) cyclization, (ii) ring transformation, (iii) aromatization as well as (iv) substituent modification, and various efficient preparations have been published.[54] We aimed at the synthesis of N^3-substituted pyrimidin-4(3*H*)-ones with a protected amino group in 5-position as well as a carboxylic acid ester in 2-position as suitable monomers. Our retrosynthetic analysis (Scheme 2) led to 4-(ethoxymethylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one **1**[55] and *N*-substituted amidines[56] of type **2** as starting materials.

Azlactone **1** deserves particular interest as a building block in heterocyclic chemistry because of its ambivalent behavior toward nucleophiles and has been utilized in various ring transformation reactions for the preparation of 5-benzoylaminopyrimidin-4(3*H*)-ones.[55,57−60] The desired 5-benzoylamino-pyrimidin-4(3*H*)-ones **3a−m** were obtained from readily available amidine hydrochloride derivatives **2a−m** and azlactone **1** by treatment with triethylamine in acetonitrile under reflux conditions (22−81% yield, Scheme 3, Table 1).

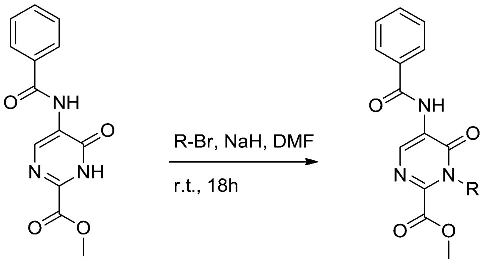
As a complementary route for the preparation of N^3-substituted monomers of type **3**, the pyrimidone **3a** (R = H) was treated with sodium hydride and alkylating agents to provide the N^3-substituted derivatives **3m,n** (32% and 64% yield, Scheme 4, Table 1). In all cases, the N^3-alkylated products were obtained as the major regioisomers. An authentic sample of **3m** obtained by azlactone rearrangement was used for structural assignment. Utilizing these protocols allows the

Table 1. Monomers Synthesized

entry	alkyl	R	yield [%]
3a	Me	H	50
3b	Me	3-indolylethyl	65
3c	Et	isobutyl	31
3d	Et	*sec*-butyl	22
3e	Et	*N*-Boc-4-aminobutyl	33
3f	Et	2-propyl	30
3g	Et	4-hydroxyphenylethyl	55
3h	Et	4-methoxyphenylethyl	41
3i	Et	4-hydroxybenzyl	52
3j	Et	4-methoxybenzyl	81
3k	Et	3-(benzyloxy)-3-oxopropyl	22
3l	Me	phenylethyl	35
3m	Me	2-(*tert*-butyl)-2-oxoethyl	49, (32)[a]
3n	Me	4-methoxybenzyl	(64)[a]

[a] Yield from *N*-alkylation.

Scheme 4. Synthesis of Monomers 3m,n by Alkylation



3a

3m: R= 2-(*tert*.-Butyl)-2-oxoethyl
3n: R= 4-Methoxybenzyl

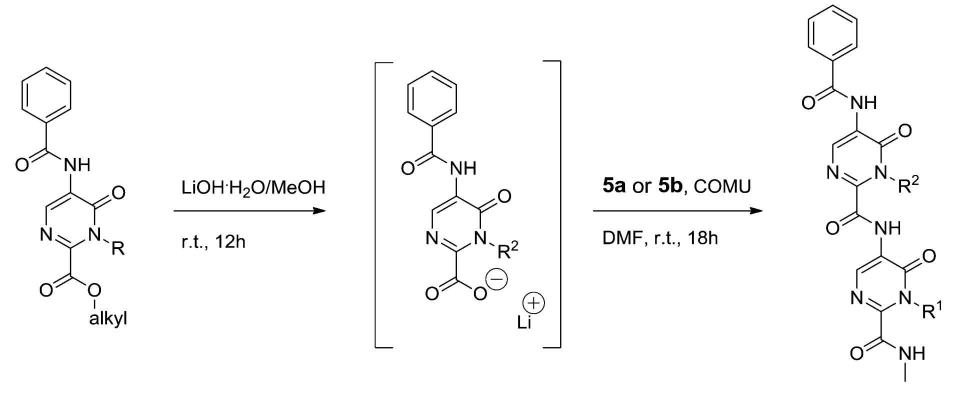
preparation of a variety of monomers with a high structural diversity with regard to the nature of the N^3-substitution. Notably, the monomers obtained are capable of mimicking aliphatic, aromatic, heteroaromatic, acidic, and basic side chains of amino acids.

After the establishment of efficient methods for preparation of the desired protected monomers **3** we studied the deprotection of both protecting groups. All attempts to deprotect the benzoyl protecting group led to the corresponding decarboxylated product. Consequently, we transformed **3b**,**c** into the *N*-methyl carboxamide derivatives **4a**,**b** utilizing an excess of methylamine as nucleophile to furnish a stable C-terminus (Scheme 3). The preparation of the unprotected 5-aminopyrimidones **5a**,**b** was achieved by saponification of the benzamide group of **4a**,**b** through treatment with sodium hydroxide (3 equiv) in methanol under reflux conditions. The attempted conversion of the alkyl ester moiety of **3** into the free carboxylic acid resulted again in isolation of the corresponding decarboxylated product. A literature survey revealed that only few pyrimidone derivatives are known with a carboxamide moiety in 2-position. These compounds were either obtained by direct treatment of an ester with a strong nucleophile or under trimethylaluminium-mediated coupling conditions. Our efforts to obtain a dimeric compound by Me_3Al-mediated coupling of the ester **3d** with the free amine **5b** failed.

As a consequence, we developed a straightforward protocol for preparation of oligomeric pyrimidone compounds. The hydrolysis of **3c**−**f** provided the corresponding lithium salts. Next, we investigated the formation of an amide bond in order to obtain dimeric pyrimidone derivatives. Several well-established coupling agents were screened using 5-aminopyrimidone **5b** and the corresponding lithium salt of **3d** as a model system. In all cases the progress of the reaction was monitored by HPLC (see Supporting Information for details). The results gathered from this screening were particularly interesting. The reaction was slow and we were unable to obtain a conversion of more than 50% after 24 h utilizing PyBop, HBTU, and DIC/Oxyma as coupling agents. The HATU-mediated amide coupling accomplished a conversion of 78% after 24 h, and the model dimer **6a** was obtained in 55% yield after purification by flash column chromatography. Best results were achieved using COMU as a coupling agent. In this case, the reaction was essentially completed after 3 h, and we were able to isolate the desired dimeric compound **6a** in 85% yield (see Supporting Information).

Having an efficient monomer synthesis and an optimized coupling reaction in hand, we turned our attention toward the preparation of dimeric and trimeric N^3-substituted pyrimidonamides as α-helix mimetics. The COMU-mediated coupling reactions of 5-aminopyrimidones **5a** and **5b** with the corresponding lithium salts of **3c** and **3d** provided smoothly the benzoyl-protected dimers **6a** and **6b** in a batch scale (75 and 76% yield, Scheme 5, Table 2). The benzoyl-protecting groups were then cleaved by treatment of **6a** and **6b** with sodium hydroxide to afford the deprotected dimers **7a** and **7b**

Scheme 5. Synthesis of Dimers 6a,b



3c: R= Isobutyl
3d: R= *sec*-Butyl

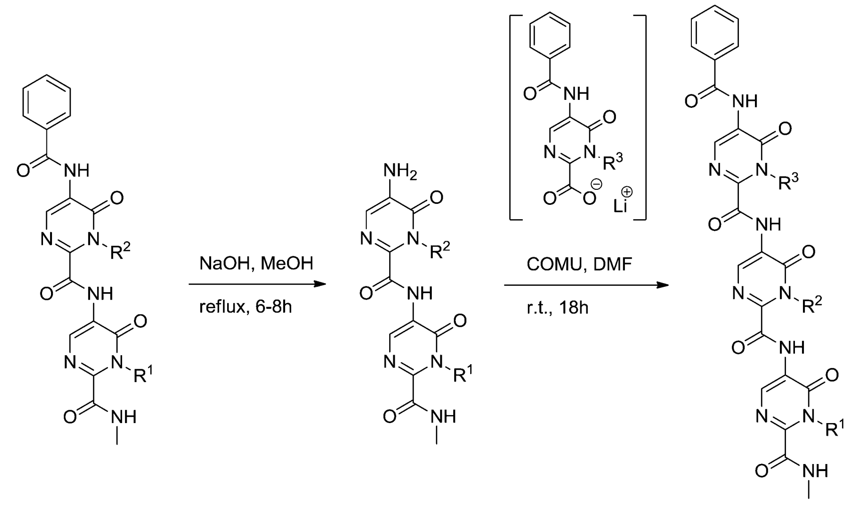
6a: R^1= Isobutyl, R^2= *sec*-Butyl
6b:R^1= 3-Indolylethyl, R^2= Isobutyl

Table 2. Synthesized Di- and Trimeric Pyrimidones

entry	R^{1a}	R^{2a}	R^{3a}	yield [%]
7a	Isobutyl “Leu”	*sec*-Butyl “Ile”	–	77
7b	3-Indolylethyl “Trp”	Isobutyl “Leu”	–	74
8a	Isobutyl “Leu”	*sec*-Butyl “Ile”	2-Propyl “Val”	55
8b	3-Indolylethyl “Trp”	Isobutyl “Leu”	*N*-Boc-4-aminobutyl “BOC-Lys”	41
8c	3-Indolylethyl “Trp”	Isobutyl “Leu”	4-Aminobutyl “Lys”	90^b

[a]Residues corresponding to mimicked amino acids. [b]From **8b** by TFA mediated cleavage of BOC protecting group.

Scheme 6. Synthesis of Trispyrimidonamides 8a,b



6a: R^1= Isobutyl, R^2= *sec*-Butyl
6b: R^1= 3-Indolylethyl, R^2= Isobutyl

7a: R^1= Isobutyl, R^2= *sec*-Butyl
7b: R^1= 3-Indolylethyl, R^2= Isobutyl

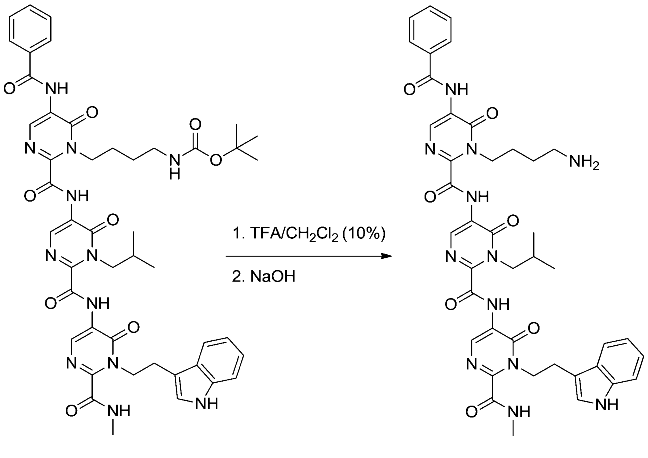
8a: R^1= Isobutyl, R^2= *sec*-Butyl, R^3= Isopropyl
8b: R^1= 3-Indolylethyl, R^2= Isobutyl, R^3= *N*-Boc-4-aminobutyl

in 77 and 74% yield, respectively (Scheme 6, Table 2). Subsequently, the reaction of **7a** and **7b** with corresponding lithium salts of **3f** and **3e** in the presence of COMU led to the corresponding trispyrimidonamides **8a** and **8b** (55% and 41% yield, Scheme 6, Table 2).

Finally, the Boc-protecting group in **8b** was removed by acidolysis to furnish trimer **8c** (Scheme 7, 90% yield) with unprotected 4-aminobutyl and 3-indolylethyl side chains, thus highlighting the versatility of our synthetic protocol in regard to side chain tolerance.

The conformational properties of our synthesized trispyrimidonamides were studied by X-ray analysis of trimer **8a** and 2D NMR spectroscopy (Figure 1). Diffraction quality crystals were obtained by vapor diffusion (see Supporting Information). The X-ray structure of **8a** (Figure 1A) shows the trimer adopting a conformation $\mathbf{C_1}$ in which only R^1 and R^3 are oriented on the same side, whereas R^2 points in the opposite direction. In order to study the properties of **8a** in solution, a ROESY experiment was performed in $CDCl_3$ (see Figure 1B and Figure S1, Supporting Information). All relevant signals were assigned by HSQC and HMBC spectra. Key ROE correlations are shown as arrows in Figure 1B. We observed ROE cross peaks between the pyrimidone proton of ring B with the methine and methyl protons of the isopropyl side chain. We reasoned that these ROE correlations would only be observable for a conformation $\mathbf{C_1}$ (Figure 1B), which is in a good agreement with the X-ray structure of **8a** (Figure 1A).

Scheme 7. Deprotection of 8b to the Corresponding Amine



8b

8c

Unfortunately, **8a–c** were not sufficiently soluble to perform a 2D NMR study in D_2O. However, we were able to study the conformational properties of the TFA salt of **8c** in methanol-d_4. We observed ROE cross signals between the isobutyl side chain and the pyrimidone protons of the two terminal rings (rings A and C), which indicates the presence of a conformation $\mathbf{C_1}$, analogous to the conformation observed in $CDCl_3$ (Figure 2 and Figures S2 and S3, Supporting Information). Interestingly, our ROESY analysis revealed an additional ROE cross peak between the methyl protons of the isobutyl side chain and the

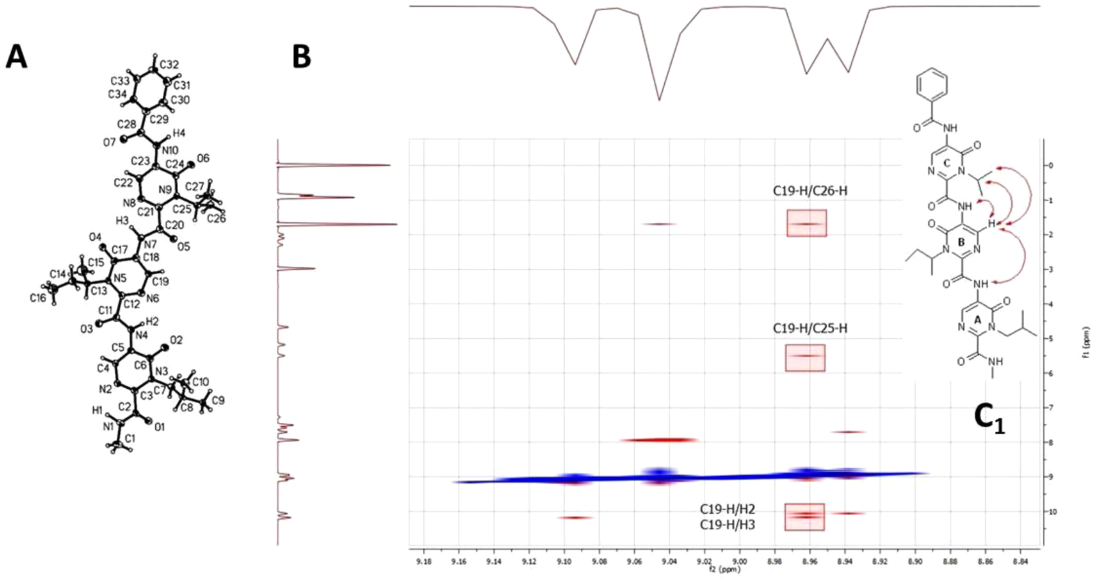


Figure 1. Structural and conformational study of compound **8a**. (A) Solid state structure. (B) $^1H-^1H$-ROESY spectra (region between 9.18 and 8.84 Hz, 600 MHz, $CDCl_3$) and suggested conformational structure; key ROEs are marked in red.

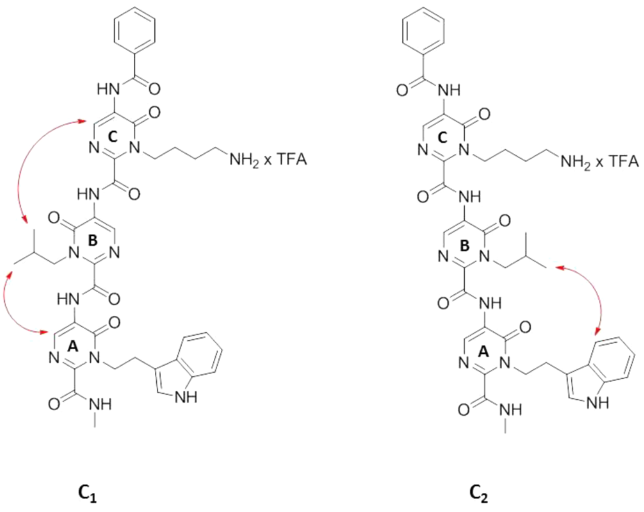


Figure 2. Conformations of **8c** (TFA salt) in MeOH-d_4. Key ROEs are marked in red.

aromatic C4-proton of the indolylethyl side chain. This ROE correlation can only be explained by a conformation $\mathbf{C_2}$ presenting all three side chains on one side (Figure 2 and Figure S3, Supporting Information). These results suggest that in methanol-d_4 trispyrimidonamides can adopt two conformations, one in which only R^1 and R^3 are oriented on the same side and one in which all three substituents are oriented on the same side.

Modeling Studies. In order to further resolve the conformational preferences of trispyrimidonamides, we performed molecular dynamics (MD) simulations of a trimethyl-substituted trispyrimidonamide (**IV**; Figure 3A) in explicit chloroform and methanol of 1.5 μs length, respectively. Prior to this, the torsion angles ϕ and ψ (Figure S4A, Supporting Information) expected to be critical for the inter-ring orientation had been parametrized based on ab initio calculations (see Experimental Section and Figure S5, Supporting Information). The energy minima of these potentials show good agreement with ϕ and ψ values found in the crystal structure of **8a** (Figure S4B, Supporting Information).

During the MD simulations, frequent rotations around the ϕ and ψ torsion angles are observed (data not shown), demonstrating that the sampled conformations are in equilibrium. This is also confirmed by the symmetry of the maps of the relative free energy of **IV** as a function of the orientation of the methyl substituents of rings A and B (torsion angle Ω_1; Figure 3A), and B and C (torsion angle Ω_2; Figure 3A) (Figure 3B). The relative free energy map for the simulation of **IV** in chloroform reveals a preferred conformation $\mathbf{C_1}$ ($\Omega_1 \approx \pm 165°$; $\Omega_2 \approx \pm 155°$; Figure 3B,C). The alternative conformation $\mathbf{C_2}$ ($\Omega_1 \approx \pm 55°$; $\Omega_2 \approx \pm 55°$) is energetically disfavored by $\Delta G \approx 2.5$ kcal mol^{-1} in chloroform. This relates to a ratio of 98.5/1.5 for the populations of $\mathbf{C_1}$ versus $\mathbf{C_2}$ in the conformational ensemble at 300 K. In contrast, the simulation of **IV** in methanol reveals $\mathbf{C_2}$ as the preferred conformation (Figure 3B,D) whereas $\mathbf{C_1}$ is now disfavored by $\Delta G \approx 1.0$ kcal mol^{-1}. This relates to a ratio of 19/81 for the populations of $\mathbf{C_1}$ versus $\mathbf{C_2}$ in the conformational ensemble at 300 K. These results are in excellent agreement with those from the 2D-NMR studies, which identified only $\mathbf{C_1}$ as the preferred conformation of **8a** in chloroform but suggested that **8c** can adopt both conformations $\mathbf{C_1}$ and $\mathbf{C_2}$ in methanol. In addition, the MD simulations confirm for $\mathbf{C_1}$ an almost coplanar orientation of the pyrimidone rings, as found in the crystal structure of **8a**, but suggest for $\mathbf{C_2}$ that neighboring rings are rotated by 55° with respect to each other. In all, these results validate our setup of the MD simulations and the quality of the force-field parameters used for the solute and solvent.

As no experimental information is available for the conformational preference of trispyrimidonamides in water, we investigated by MD simulations in explicit water the conformational preference of **IV** using the same setup as above. The MD simulations suggest that $\mathbf{C_2}$ becomes even more preferred over $\mathbf{C_1}$ than in methanol (Figure 3B,D), with $\mathbf{C_1}$ being disfavored by $\Delta G \approx 3.0$ kcal mol^{-1} equivalent to a ratio of <1/99 for the populations of $\mathbf{C_1}$ versus $\mathbf{C_2}$ in the conformational ensemble at 300 K. This shift in the

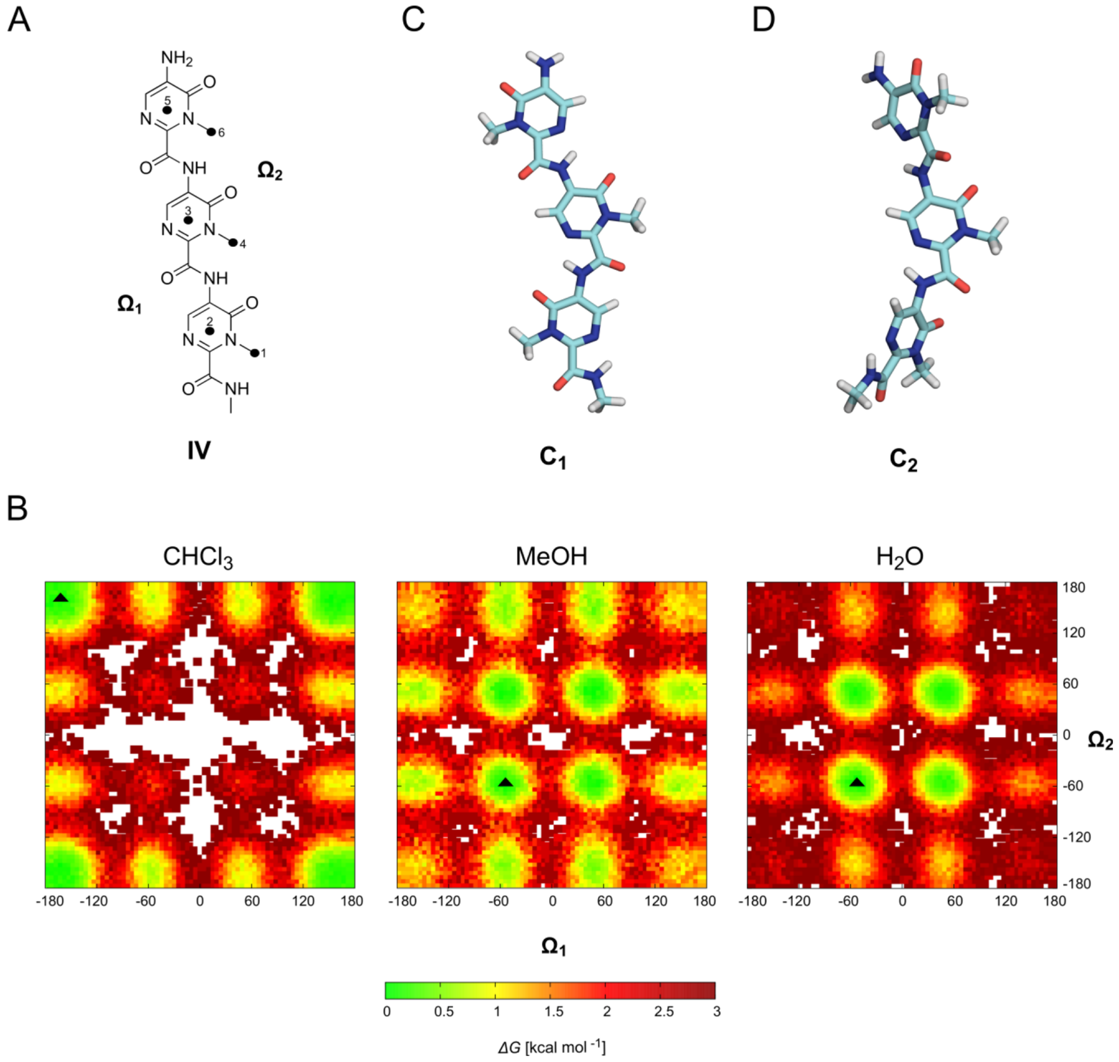


Figure 3. Relative free energy of the trimethylsubstituted trispyrimidonamide **IV** as a function of the orientation of the methyl substituents of rings A and B, or B and C, with respect to each other (Ω_1 and Ω_2 torsion angles as defined by the point quadruples (1, 2, 3, 4) and (4, 3, 5, 6) in the structure shown in panel A). The relative free energy of each conformation is calculated from the frequency of the conformation's occurrence during a MD simulation of 1.5 μs length in explicit chloroform, explicit methanol, and explicit water (see respective plots in panel B) via $\Delta G = -RT \ln P_x/P_{\text{ref}}$ (where R is the gas constant, T = 300 K, P_x is the frequency of occurrence of conformation x, and P_{ref} is the frequency of occurrence of the most frequently represented conformation). The white spots indicate Ω_1 and Ω_2 angle combinations not found in the MD simulations. Energetically favorable conformations of **IV** in the different solvents are shown in panel C (chloroform; $\mathbf{C_1}$) and D (methanol and water; $\mathbf{C_2}$); their locations on the relative free energy maps are marked by triangles.

conformational equilibrium agrees with the solvent influence on the conformations of trispyrimidonamides observed by our 2D NMR studies in chloroform and methanol in that more polar solvents favor $\mathbf{C_2}$.

Overlaying the methyl groups of **IV** in the conformation $\mathbf{C_2}$ favored in polar solvents with the C_β atoms of a canonical α-helix shows that the trispyrimidonamide scaffold can closely mimic the spatial arrangement of peptide side chains at positions *i*, *i* + 4, *i* + 8. When ring C is oriented toward the helix C-terminus, the root mean-square deviation (RMSD) of the coordinates of the respective atom pairs is 0.69 Å, and the average angle deviation between the respective bond vectors is ~20° (Figure 4A). These values deteriorate to 0.73 Å and ~30° if ring C is oriented toward the N-terminus (Figure 4B). To the best of our knowledge, there is only one other scaffold of α-helix mimetics that allows addressing the side chain pattern *i*, *i* + 4, *i* + 8;[53] this pattern becomes particularly interesting if the side chains to be mimicked lie on one side of an α-helix but are distributed over a wider angular range than in the case of *i*, *i* + 4, *i* + 7.[61] Alternatively, two of the methyl groups of conformation $\mathbf{C_1}$ can overlay with C_β atoms of a canonical α-helix at positions *i* and *i* + 8 (when ring C is oriented toward the C(N)-terminus the RMSD = 0.2 Å (0.55 Å), and the average angle deviation between bond vectors is ~10° (~38°)) (Figure 4C,D). The *i*, *i* + 8 pattern would be of interest when two side chains further apart but still on the same side of an α-helix need to be mimicked. Targeting a *i*, *i* + 4, *i* + 7 side chain pattern with our trispyrimidonamides is expected to be less favorable but not excluded, as demonstrated by the increased RMSD and average angle deviations between bond vectors when overlaying the methyl groups of $\mathbf{C_1}$ or $\mathbf{C_2}$ with the C_β atoms of a canonical α-helix at these positions (see Supporting Information, Figure S6).

In summary, the conformational analyses by 2D NMR studies and MD simulations reveal that trispyrimidonamides adopt conformations in polar solvents that can lead to *i*, *i* + 4,

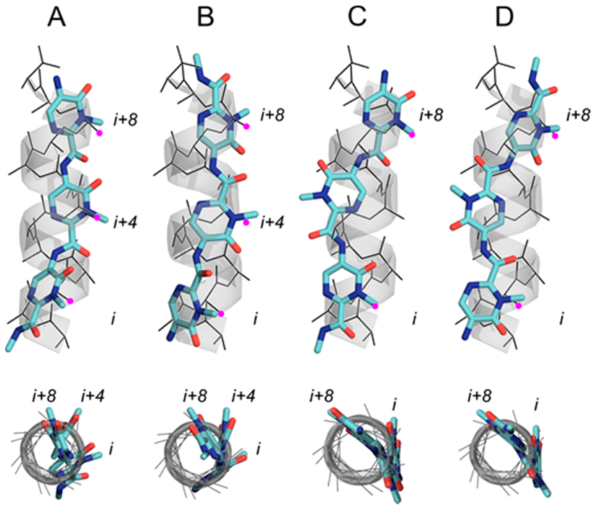


Figure 4. Overlay of C_β atoms of a canonical α-helix onto corresponding methyl groups of **IV** in conformation $\mathbf{C_2}$ (A), resulting in an i, $i + 4$, $i + 8$ pattern, and $\mathbf{C_1}$ (C), resulting in an i, $i + 8$ pattern. Ring C is oriented toward the C-terminus of the helix. (B,D) Equivalent superimpositions when **IV** is reversed with respect to the helix axis. The magenta dots highlight the C_β atoms addressed by the trispyrimidonamide's R groups. In the lower panel the overlays are rotated by 90°, with the peptide C-terminus oriented in the direction of the viewer.

$i + 8$ or i, $i + 8$ patterns of R-group orientation with respect to an α-helix.

■ CONCLUSIONS

In summary, we have established a straightforward preparation of 5-benzoylaminopyrimidin-4(3*H*)-one monomers capable of mimicking aliphatic, aromatic, heteroaromatic, and basic side chains of amino acids. A COMU-mediated coupling procedure allowed the synthesis of trispyrimidonamide α-helix mimetics including an example with side chains that are difficult to access, such as 4-aminobutyl and 3-indolylethyl moieties. A comprehensive conformational study by X-ray, 2D NMR analysis, and MD simulations revealed a solvent dependence of the preferred conformations of the trispyrimidonamide scaffold. In polar solvents, the trispyrimidonamide scaffold adopts conformations that can lead to i, $i + 4$, $i + 8$ or i, $i + 8$ patterns of side chain orientation. This suggests trispyrimidonamides as promising α-helix mimetics to target hot spots that lie on one side of an α-helix but are distributed over a wider angular range than in the classical i, $i + 4$, $i + 7$ case.

■ EXPERIMENTAL SECTION

Chemistry. All solvents and chemicals were used as purchased without further purification. The progress of all reactions was monitored on silica gel plates (with fluorescence indicator UV254) using the solvent system stated. Flash column chromatography was carried out using prepacked silica cartridge. Melting points (mp) were taken in open capillaries and are uncorrected. ^{1}H and ^{13}C spectra were recorded at 500 (500.13 MHz for ^{1}H; 125.76 MHz for ^{13}C) and 600 (600.22 MHz for ^{1}H; 150.92 MHz for ^{13}C) MHz spectrometers, respectively, using DMSO-d_6 or $CDCl_3$ as solvents. Chemical shifts are given in parts million (ppm), (δ relative to residual solvent peak for ^{1}H and ^{13}C or to external standard tetramethylsilane). High resolution mass spectra (HRMS) were obtained on a UHR-TOF mass analyzer by electrospray ionization (ESI). Azlactone **1** was prepared as reported.[55] Amidine hydrochlorides **2a**−**m** are prepared following a literature procedure[56] with the minor modification using 0.6 equiv of the corresponding amine hydrochloride.

General Procedure for the Synthesis of Alkyl 5-benzamido-6-oxo-1,6-dihydropyrimidine-2-carboxylates 3a−m. A mixture of 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one **1** (0.217 g, 1 mmol), the corresponding amidine hydrochloride **2a**−**m** (1 mmol) and triethylamine (0.101 g, 1 mmol) in dry acetonitrile (5 mL) was heated under a nitrogen atmosphere for 3 h (**3a**,**c**,**d**,**f**) or 6 h. The solvent was removed under reduced pressure, and aqueous citric acid (10 wt %, 3 mL) was added. The mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in a vacuum. The crude products were purified by flash column chromatography (gradient: 10:90 → 30:70 ethyl acetate:*n*-hexane) to yield the desired products **3a**−**m**.

*Methyl 5-benzamido-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3a**).* Yield 50%, 137 mg, pale white solid: $R_f = 0.42$ (ethyl acetate); mp 209 °C (from ethyl acetate/methanol); ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.51 (s, 1H), 9.47 (s, 1H), 8.86 (s, 1H), 7.95 (d, $J = 7.2$ Hz, 2H), 7.64 (t, $J = 7.4$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.3, 159.9, 133.1, 132.3, 128.7, 127.5, 53.2, 40.0. Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 56.91; H, 4.02; N 15.24.

*Methyl 1-(2-(1H-indol-3-yl)ethyl)-5-benzamido-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3b**).* Yield 65%, 270 mg, pale yellow solid: $R_f = 0.56$ (*n*-hexane/ethyl acetate 1:1); mp 222 °C (from ethyl acetate); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (s, 1H), 9.62 (s, 1H), 8.79 (s, 1H), 8.00 (d, $J = 7.4$ Hz, 2H), 7.69−7.51 (m, 4H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.06 (ddd, $J = 7.3$, 14.8, 22.2 Hz, 3H), 4.42 (t, $J = 7.1$ Hz, 2H), 3.46 (s, 3H), 3.12 (t, $J = 7.0$ Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.4, 160.4, 156.7, 144.0, 136.4, 136.3, 133.1, 132.3, 128.7, 127.6, 127.5, 126.8, 123.7, 121.1, 118.4, 118.0, 111.4, 109.3, 53.0, 46.2, 23.8. Anal. Calcd. for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.45. Found: C, 66.13; H, 4.92; N 13.54.

*Ethyl 5-benzamido-1-isobutyl-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3c**).* Yellow solid, yield 31%, 106 mg: $R_f = 0.89$ (*n*-hexane/ethyl acetate 1:1); mp 59 °C (from diethyl ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.96 (s, 1H), 7.93 (d, $J = 8.1$ Hz, 2H), 7.59 (t, $J = 7.8$ Hz, 1H), 7.51 (t, $J = 7.7$ Hz, 2H), 4.48 (q, $J = 7.1$ Hz, 2H), 4.25 (d, $J = 7.5$ Hz, 2H), 2.08−2.02 (m, 1H), 1.45 (t, $J = 7.2$ Hz, 3H), 0.94 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 160.9, 157.6, 143.3, 134.6, 133.4, 132.6, 128.9, 127.9, 127.3, 63.4, 51.7, 28.6, 19.9, 14.0. Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.91; H, 6.30; N 12.22.

*Ethyl 5-benzamido-1-(sec-butyl)-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3d**).* Yield 22%, 75 mg, yellow oil: $R_f = 0.90$ (*n*-hexane/ethyl acetate 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.95 (s, 1H), 7.93 (d, $J = 7.2$ Hz, 2H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 2H), 4.48 (m, 2H), 4.16 (s, 1H), 2.30 (dt, $J = 7.7$, 15.1 Hz, 1H), 1.94−1.89 (m, 1H), 1.66 (d, $J = 6.8$ Hz, 3H), 1.45 (t, $J = 7.2$ Hz, 3H), 0.87 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 161.3, 157.4, 144.9, 134.5, 133.4, 132.5, 128.9, 128.0, 127.3, 63.3, 61.4, 26.0, 17.8, 14.0, 11.3. Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.69; H, 5.99; N 12.09.

*Ethyl 5-benzamido-1-(4-tert-butoxycarbonylaminobutyl)-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3e**).* Yield 33%, 151 mg, pale yellow solid: $R_f = 0.59$ (*n*-hexane/ethyl acetate 1:1); mp 97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.94 (s, 1H), 7.93 (d, $J = 7.3$ Hz, 2H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 2H), 4.70 (s, 1H), 4.48 (q, $J = 7.1$ Hz, 2H), 4.26−4.22 (m, 2H), 3.19 (d, $J = 6.1$ Hz, 2H), 1.87−1.84 (m, 2H), 1.60−1.57 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 160.7, 157.4, 155.9, 142.8, 134.7, 133.3, 132.6, 129.0, 128.0, 127.3, 79.2, 77.3, 63.5, 46.0, 39.8, 28.4, 27.2, 26.1, 14.0. Anal. Calcd. for $C_{23}H_{30}N_4O_6$: C, 60.25; H, 6.59; N, 12.22. Found: C, 60.16; H, 6.54; N 11.98.

*Ethyl 5-benzamido-1-isopropyl-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3f**).* Yield 30%, 98 mg, yellow solid: $R_f = 0.70$ (*n*-hexane/ethyl acetate 1:1); mp 106 °C (from ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.95 (s, 1H), 7.93 (d, $J = 7.2$ Hz, 1H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 2H), 4.52−4.46 (m, 3H), 1.82−1.57 (m, 6H), 1.45 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126

MHz, $CDCl_3$) δ 165.5, 161.3, 157.5, 144.4, 134.4, 133.4, 132.5, 128.9, 128.2, 127.3, 63.3, 55.0, 19.6, 14.0. Anal. Calcd. for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 61.83; H, 5.73; N 12.76.

*Ethyl 5-benzamido-1-(4-hydroxyphenethyl)-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3g**).* Yield 55%, 224 mg, pale yellow solid: R_f = 0.65 (*n*-hexane/ethyl acetate 1:1); mp 191 °C (from ethyl acetate); ^1H NMR (500 MHz, DMSO-d_6) δ 9.57 (s, 1H), 9.30 (s, 1H), 8.79 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.65 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.6 Hz, 2H), 6.95 (d, J = 8.3 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 4.35–4.23 (m, 4H), 2.92–2.84 (m, 2H), 1.30 (t, J = 7.1, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.4, 160.3, 156.6, 156.1, 144.1, 136.5, 133.1, 132.3, 129.6, 128.6, 127.6, 127.4, 127.3, 115.4, 62.9, 47.5, 32.9, 13.6. Anal. Calcd. for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31. Found: C, 64.71; H, 5.22; N 10.25.

*Ethyl 5-benzamido-1-(4-methoxyphenethyl)-6-oxo-1,6-dihydropyrimidin-2-carboxylate (**3h**).* Yield 41%, 173 mg, yellow oil: R_f = 0.75 (*n*-hexane/ethyl acetate 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.98 (s, 1H), 7.94 (d, J = 8.6 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.51–4.43 (m, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.06–3.00 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 160.6, 158.7, 157.4, 142.7, 134.7, 133.3, 132.6, 130.0, 129.2, 129.0, 128.0, 127.4, 114.2, 63.4, 55.2, 47.9, 33.9, 13.9. Anal. Calcd. for $C_{23}H_{23}N_3O_5$: C, 65.55; H, 5.50; N, 9.97. Found: C, 65.71; H, 5.72; N 9.70.

*Ethyl 5-benzamido-1-(4-hydroxybenzyl)-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3i**).* Pale yield 52%, 204 mg, yellow solid: R_f = 0.56 (*n*-hexane/ethyl acetate 1:1); mp 166 °C (from ethyl acetate); ^1H NMR (500 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.49 (s, 1H), 8.79 (s, 1H), 7.96 (d, J = 7.3 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 7.04 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 5.27 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.4, 160.4, 157.0, 156.7, 144.7, 136.8, 133.0, 132.3, 128.9, 128.6, 127.6, 127.4, 125.6, 115.2, 62.8, 47.3, 13.5. Anal. Calcd. for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 63.91; H, 4.89; N 10.97.

*Ethyl 5-benzamido-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3j**).* Yield 81%, 329 mg, yellow oil: R_f = 0.72 (*n*-hexane/ethyl acetate 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.96 (s, 1H), 7.92 (d, J = 8.6 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.54 (s, 2H), 4.35 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 160.9, 159.5, 157.6, 143.1, 134.8, 133.3, 132.6, 129.5, 128.9, 128.1, 127.4, 127.3, 114.2, 63.3, 55.3, 47.6, 13.9. Anal. Calcd. for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31. Found: C, 64.64; H, 5.42; N 10.02.

*Ethyl 5-benzamido-1-(3-(benzyloxy)-3-oxopropyl)-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3k**).* Yield 22%, 99 mg, yellow solid: R_f = 0.73 (*n*-hexane/ethyl acetate 1:1); mp 96 °C (from ethyl acetate) ^1H NMR (600 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.89 (s, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.37–7.25 (m, 5H), 5.13 (s, 2H), 4.56 (t, J = 7.1 Hz, 2H), 4.49–4.46 (m, 2H), 2.97 (t, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 165.6, 160.7, 157.5, 142.9, 135.4, 134.7, 133.3, 132.6, 129.0, 128.6, 128.5, 128.4, 128.0, 127.3, 66.8, 63.5, 42.5, 32.6, 14.0. Anal. Calcd. for $C_{24}H_{23}N_3O_6$: C, 64.13; H, 5.16; N, 9.35. Found: C, 64.40; H, 5.16; N 9.36.

*Methyl 5-benzamido-6-oxo-1-phenethyl-1,6-dihydropyrimidine-2-carboxylate (**3l**).* Yield 35%, 132 mg, orange solid: R_f = 0.67 (*n*-hexane/ethyl acetate 1:1); mp 115 °C (from ethyl acetate); ^1H NMR (500 MHz, DMSO-d_6) δ 9.60 (s, 1H), 8.81 (s, 1H), 7.98 (d, J = 7.3 Hz, 2H), 7.65 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.20 (d, J = 7.2 Hz, 2H), 4.43–4.22 (m, 2H), 3.86 (s, 3H), 3.12–2.87 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.4, 160.8, 156.6, 143.8, 137.5, 136.3, 133.0, 132.3, 128.7, 128.6, 128.5, 127.7, 127.6, 126.7, 53.5, 47.4, 39.9, 39.8, 39.6, 39.4, 39.3, 33.8. Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.65; H, 5.09; N 11.14.

*Methyl 5-benzamido-1-(2-(tert-butoxy)-2-oxoethyl)-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3m**).* Yield 49%, 189 mg, pale white solid: R_f = 0.63 (*n*-hexane/ethyl acetate 1:1); mp 192 °C (from ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.94 (s, 1H), 7.92 (d, J = 8.6 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 5.21 (s, 2H), 3.98 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 165.7, 161.0, 157.5, 140.7, 134.3, 133.2, 132.7, 129.0, 128.4, 127.4, 83.5, 53.9, 46.5, 28.0. Anal. Calcd. for $C_{19}H_{21}N_3O_6$: C, 58.91; H, 5.46; N, 10.84. Found: C, 58.71; H, 5.56; N 10.66.

General Procedure for Synthesis of Alkyl 5-benzamido-6-oxo-1,6-dihydropyrimidine-2-carboxylates 3m,n. Pyrimidone **3a** (0.273 g, 1 mmol) was dissolved in absolute DMF (1 mL) under nitrogen atmosphere. Sodium hydride (40 mg, 1 mmol, 60% in mineral oil) was added, and the mixture was stirred for one hour at room temperature. The appropriate alkylating agent (1.2 mmol) was added slowly, and the resulting solution was stirred overnight. The reaction was quenched by addition of saturated sodium chloride solution (2 mL) and extracted with ethyl acetate (3 × 5 mL). The solvent was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by flash column chromatography (gradient: 10:90 → 30:70 ethyl acetate:*n*-hexane) to give monomers **3n,m**.

*Methyl 5-benzamido-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidine-2-carboxylate (**3n**).* Yield 64%, 251 mg, yellow solid: mp 101 °C (from ethyl acetate); R_f = 0.73 (*n*-hexane/ethyl acetate 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.98 (s, 1H), 7.92 (d, J = 7.4 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 5.55 (s, 2H), 3.89 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 161.3, 159.5, 157.6, 142.5, 134.6, 133.3, 132.6, 129.5, 128.9, 128.3, 127.4, 127.3, 114.2, 55.3, 53.7, 47.6. Anal. Calcd. for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 63.94; H, 4.85; N 10.67.

General Procedure for the Synthesis of 5-Benzamido-*N*-methyl-6-oxo-1,6-dihydropyrimidine-2-carboxamide 4a,b. An aqueous solution of methylamine (40 wt %, 2 mL) was added dropwise to a cooled mixture of the corresponding ester **3b**,**c** (1 mmol) in ethanol (2 mL). The ice bath was removed, and the reaction was stirred at room temperature until TLC (1:1 ethyl acetate:*n*-hexane) showed complete conversion of the starting material. Water (10 mL) was added, and the crude amide was filtered off and recrystallized from an appropriate solvent to afford amides **4a**,**b**.

*1-(2-(1H-Indol-3-yl)ethyl)-5-benzamido-N-methyl-6-oxo-1,6-dihydropyrimidine-2-carboxamide (**4a**).* Yield 90%, 373 mg, pale white solid: R_f = 0.32 (*n*-hexane/ethyl acetate 1:1); mp 270 °C (from THF); ^1H NMR (500 MHz, DMSO-d_6) δ 10.89 (s, 1H), 9.58 (s, 1H), 8.84 (d, J = 4.6, 1H), 8.78 (s, 1H), 8.00 (d, J = 7.4 Hz, 2H), 7.71 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.5 Hz, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.16 (s, 1H), 7.09 (t, J = 7.4 Hz, 1H), 7.02 (t, J = 7.3 Hz, 1H), 4.57–4.28 (m, 2H), 3.20–3.06 (m, 2H), 2.73 (d, J = 4.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.4, 161.3, 157.1, 147.9, 137.2, 136.2, 133.2, 132.2, 128.6, 127.5, 126.9, 126.5, 123.1, 121.0, 118.3, 118.2, 111.4, 110.0, 46.0, 25.8, 24.5. Anal. Calcd. for $C_{23}H_{21}N_5O_3$: C, 66.49; H, 5.09; N, 16.86. Found: C, 66.32; H, 4.86; N 16.69.

*5-Benzamido-1-isobutyl-N-methyl-6-oxo-1,6-dihydropyrimidine-2-carboxamide (**4b**).* Yield 89%, 292 mg, white solid: R_f = 0.59 (*n*-hexane/ethyl acetate 1:1); mp 128 °C (from ethyl acetate); ^1H NMR (500 MHz, DMSO-d_6) δ 9.48 (s, 1H), 9.01 (d, J = 4.7 Hz, 1H), 8.76 (s, 1H), 7.99–7.93 (m, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 4.18 (d, J = 7.4 Hz, 2H), 2.78 (d, J = 4.7 Hz, 3H), 2.07–1.99 (m, 1H), 0.85 (d, J = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.3, 161.6, 157.3, 147.9, 136.9, 133.2, 132.2, 128.6, 127.5, 126.4, 50.6, 27.6, 25.8, 19.6. Anal. Calcd. for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06. Found: C, 62.00; H, 6.01; N 17.01.

General Procedure for the Synthesis of Monomeric 5-Amino Pyrimidonamides (5a,b). A mixture of the respective benzamide **4a**,**b** (1 mmol) and sodium hydroxide (0.12 g, 3 mmol) in methanol (3 mL) was heated for 6 h (**4b**) or 8 h (**4a**). The solvent was removed under reduced pressure, water (5 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under a vacuum. The crude residues were purified by flash column chromatography (gradient: 30:70 → 100:0 ethyl acetate:*n*-hexane) to yield the desired products **5a**,**b**.

*1-(2-(1H-Indol-3-yl)ethyl)-5-amino-N-methyl-6-oxo-1,6-dihydropyrimidine-2-carboxamide (**5a**).* Yield 92%, 286 mg, pale yellow solid: $R_f = 0.10$ (*n*-hexane/ethyl acetate 1:1); mp 196 °C (from ethyl acetate); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.54 (s, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.23 (s, 1H), 7.14 (s, 1H), 7.08 (t, $J = 7.4$ Hz, 1H), 7.00 (t, $J = 7.4$ Hz, 1H), 5.61 (s, 2H), 4.53−4.40 (m, 2H), 3.12−3.03 (m, 2H), 2.70 (d, $J = 4.4$ Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.9, 156.9, 139.8, 136.2, 136.1, 127.0, 122.9, 122.6, 120.9, 118.4, 118.2, 111.3, 110.6, 45.0, 25.8, 24.8. Anal. Calcd. for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 61.53; H, 5.57; N 22.31.

*5-Amino-1-isobutyl-N-methyl-6-oxo-1,6-dihydropyrimidine-2-carboxamide (**5b**).* Yield 88%, 197 mg, pale white solid: $R_f = 0.21$ (*n*-hexane/ethyl acetate 1:1); mp 127 °C (from ethyl acetate); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H), 7.20 (s, 1H), 5.54 (s, 2H), 4.26 (d, $J = 7.3$ Hz, 2H), 2.71 (d, $J = 4.4$ Hz, 3H), 1.93 (s, 1H), 0.79 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2, 157.2, 139.7, 134.0, 122.4, 49.3, 27.8, 25.8, 19.6. Anal. Calcd. for $C_{10}H_{16}N_4O_2$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.48; H, 7.19; N 24.95.

General Procedure for Synthesis of Dimeric Pyrimidonamides (6a,b). A mixture of the appropriate alkyl 5-benzamido-6-oxo-1,6-dihydropyrimidine-2-carboxylate (1.5 equiv) and lithium hydroxide hydrate (1.5 equiv) were dissolved in methanol and stirred for 12 h. The solvent was removed under a vacuum using an ice cooled water bath. The resulting yellow oil was treated with dry diethyl ether to crystallize. The precipitate was collected, dried under a vacuum, and transferred into a two-neck round-bottom flask containing the appropriate 5-amino pyrimidonamide **5a**,**b** (1 equiv) and COMU (1.8 equiv). The starting materials were dissolved in dry DMF (1 mL per mmol) and stirred for 18 h under nitrogen atmosphere. Dichloromethane (30 mL) was added, and the organic layer was washed with saturated sodium hydrogen carbonate solution (10 mL), 10% aqueous citric acid solution (10 mL) and brine (10 mL). After drying over sodium sulfate the organic layer was concentrated in a vacuum. The residue was crystallized by treatment with dry diethyl ether and recrystallized from an appropriate solvent.

*5-Benzamido-1-(sec-butyl)-N-(1-isobutyl-2-methylcarbamoyl-6-oxo-1,6-dihydropyrimidin-5-yl)-6-oxo-1,6-dihydropyrimidine-2-carboxamide (**6a**).* Yield 75%, 390 mg, pale yellow solid: $R_f = 0.68$ (*n*-hexane/ethyl acetate 1:1); mp 155 °C (from dichloromethane); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.74 (s, 1H), 9.48 (s, 1H), 8.99 (d, $J = 4.7$ Hz, 1H), 8.80 (s, 1H), 8.75 (s, 1H), 7.98 (d, $J = 7.4$ Hz, 2H), 7.64 (t, $J = 7.4$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 2H), 4.35−4.34 (m, 1H), 4.16 (d, $J = 7.4$ Hz, 2H), 2.79 (d, $J = 4.7$ Hz, 3H), 2.20 (dt, $J = 7.5$, 14.6 Hz, 1H), 2.03 (dt, $J = 6.9$, 13.7 Hz, 1H), 1.92 (dt, $J = 7.2$, 14.0 Hz, 1H), 1.57 (d, $J = 6.7$ Hz, 3H), 0.85−0.81 (m, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.2, 161.5, 160.5, 157.1, 156.7, 148.6, 147.9, 137.0, 136.5, 133.1, 132.2, 128.6, 127.5, 127.1, 125.8, 59.9, 50.6, 27.6, 25.8, 25.4, 19.6, 17.1, 11.0. Anal. Calcd. for $C_{26}H_{31}N_7O_5$: C, 59.87; H, 5.99; N, 18.80. Found: C, 59.61; H, 5.97; N 18.80.

*1-(2-(1H-Indol-3-yl)ethyl)-5-(5-benzamido-1-isobutyl-6-oxo-1,6-dihydropyrimidine-2-carboxamido)-N-methyl-6-oxo-1,6-dihydropyrimidine-2-carboxamide (**6b**).* Yield 76%, 462 mg, pale yellow solid: $R_f = 0.29$ (*n*-hexane/ethyl acetate 1:1); mp 267 °C (from ethyl acetate); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.90 (s, 1H), 10.71 (s, 1H), 9.59 (s, 1H), 8.86 (s, 1H), 8.81 (s, 1H), 8.00 (d, $J = 7.2$ Hz, 2H), 7.72−7.63 (m, 2H), 7.58 (t, $J = 7.6$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 1H), 7.17 (d, $J = 2.1$ Hz, 1H), 7.10 (t, $J = 7.2$ Hz, 1H), 7.02 (t, $J = 7.2$ Hz, 1H), 4.47−4.36 (m, 2H), 4.28 (d, $J = 7.3$ Hz, 2H), 3.18−3.08 (m, 2H), 2.73 (d, $J = 4.7$ Hz, 3H), 2.18−2.06 (m, 1H), 0.91 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.4, 161.2, 159.3, 157.4, 156.6, 148.3, 145.4, 136.2, 136.1, 133.1, 132.3, 128.6, 127.6, 127.0, 126.9, 125.9, 123.2, 121.0, 118.3, 118.2, 111.4, 110.0, 50.8, 46.1, 38.1, 28.0, 25.8, 24.4, 19.8. Anal. Calcd. for $C_{32}H_{32}N_8O_5$: C, 63.15; H, 5.30; N, 18.41. Found: C, 62.92; H, 5.25; N 18.21.

General Procedure for the Synthesis of Dimeric 5-Amino Pyrimidonamides (7a,b). A mixture of the respective benzamide **6a**,**b** (1 mmol) and sodium hydroxide (0.12 g, 3 mmol) in methanol (3 mL) was heated for 6 h (**6a**) or 8 h (**6b**). The solvent was removed under reduced pressure, water (5 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under a vacuum. The crude residues were purified by flash column chromatography (gradient: 30:70 → 100:0 ethyl acetate:*n*-hexane) to yield the desired products **7a**,**b**.

*5-Amino-1-(sec-butyl)-N-(1-isobutyl-2-(methylcarbamoyl)-6-oxo-1,6-dihydropyrimidin-5-yl)-6-oxo-1,6-dihydropyrimidine-2-carboxamide (**7a**).* Yield 77%, 321 mg, yellow solid: $R_f = 0.50$ (*n*-hexane/ethyl acetate 1:1); mp 263 °C (from ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.93 (s, 1H), 7.74 (s, 1H), 7.32 (s, 1H), 5.29 (dd, $J = 6.9$, 14.7 Hz, 1H), 4.66 (d, $J = 7.4$ Hz, 2H), 4.57 (s, 2H), 2.98 (d, $J = 5.1$ Hz, 3H), 2.31−2.29 (m, 1H), 2.10 (dt, $J = 6.9$, 13.8 Hz, 1H), 1.96−1.94 (m, 1H), 1.68 (d, $J = 6.7$ Hz, 3H), 0.90 (dd, $J = 6.6$, 19.3 Hz, 6H), 0.83 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.1, 159.4, 158.2, 158.0, 144.3, 139.3, 136.8, 133.6, 127.3, 123.0, 58.8, 51.0, 28.8, 26.6, 25.9, 19.8, 17.9, 11.4. Anal. Calcd. for $C_{19}H_{27}N_7O_4$: C, 54.66; H, 6.52; N, 23.49. Found: C, 54.38; H, 6.56; N 23.21.

*1-(2-(1H-Indol-3-yl)ethyl)-5-(5-amino-1-isobutyl-6-oxo-1,6-dihydropyrimidine-2-carboxamido)-N-methyl-6-oxo-1,6-dihydropyrimidine-2-carboxamide (**7b**).* Yield 74%, 373 mg, yellow solid: $R_f = 0.44$ (*n*-hexane/ethyl acetate 1:1); mp 223 °C (from dichloromethane); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (s, 1H), 10.39 (s, 1H), 8.78 (d, $J = 6.1$ Hz, 2H), 7.68 (d, $J = 7.8$ Hz, 1H), 7.36 (d, $J = 10.8$ Hz, 2H), 7.15 (d, $J = 1.7$ Hz, 1H), 7.09 (t, $J = 7.5$ Hz, 1H), 7.02 (t, $J = 7.4$ Hz, 1H), 6.10 (s, 2H), 4.53−4.51 (m, 2H), 4.47−4.25 (m, 2H), 3.19−2.98 (m, 2H), 2.72 (d, $J = 4.7$ Hz, 3H), 2.04 (dd, $J = 12.9$, 19.8 Hz, 1H), 0.86 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.7, 159.3, 157.5, 157.2, 147.5, 136.7, 135.7, 134.3, 127.4, 126.7, 123.6, 121.8, 121.5, 118.8, 118.7, 111.8, 110.5, 55.3, 49.7, 46.6, 28.8, 26.2, 24.8, 20.1. Anal. Calcd. for $C_{25}H_{28}N_8O_4$: C, 59.51; H, 5.59; N, 22.21. Found: C, 59.38; H, 5.77; N 21.92.

General Procedure for Synthesis of Trimeric Pyrimidonamides (8a,b). A mixture of the appropriate alkyl 5-benzamido-6-oxo-1,6-dihydropyrimidine-2-carboxylate (1.5 equiv) and lithium hydroxide hydrate (1.5 equiv) were dissolved in methanol and stirred for 12 h. The solvent was removed under a vacuum using an ice cooled water bath. The resulting yellow oil was treated with dry diethyl ether to crystallize. The precipitate was collected, dried under a vacuum and was transferred into a two-neck round-bottom flask containing the appropriate 5-amino pyrimidonamide **7a**,**b** (1 equiv) and COMU (1.8 equiv). The starting materials were dissolved in dry DMF (1 mL per mmol) and stirred for 18 h under nitrogen atmosphere. Dichloromethane (30 mL) was added, and the organic layer was washed with saturated sodium hydrogen carbonate solution (10 mL), 10% aqueous citric acid solution (10 mL) and brine (10 mL). After drying over sodium sulfate the organic layer was concentrated in a vacuum. The residue was crystallized by treatment with dry diethyl ether and recrystallized from an appropriate solvent.

*5-Benzamido-N-(1-(sec-butyl)-2-((1-isobutyl-2-(methylcarbamoyl)-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl)-6-oxo-1,6-dihydropyrimidin-5-yl)-1-isopropyl-6-oxo-1,6-dihydropyrimidine-2-carboxamide (**8a**).* Yield 55%, 192 mg, yellow solid: $R_f = 0.66$ (*n*-hexane/ethyl acetate 1:1); mp 257 °C (from dichloromethane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.18 (s, 1H), 10.06 (s, 1H), 9.10 (s, 1H), 9.05 (s, 1H), 8.96 (s, 1H), 8.95 (s, 1H), 7.94 (d, $J = 7.3$ Hz, 2H), 7.70 (d, $J = 5.0$ Hz, 1H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.7$ Hz, 2H), 5.53−5.48 (m, 1H), 5.19 (dd, $J = 6.9$, 14.7 Hz, 1H), 4.68 (d, $J = 7.3$ Hz, 2H), 2.99 (d, $J = 5.1$ Hz, 3H), 2.31−2.29 (m, 1H), 2.11−2.09 (m, 1H), 2.01 (dd, $J = 7.1$, 14.1 Hz, 1H), 1.70 (t, $J = 10.0$ Hz, 9H), 0.93 (dd, $J = 1.6$, 6.7 Hz, 6H), 0.87 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.6, 160.9, 158.8, 158.8, 158.3, 157.9, 157.8, 145.0, 144.8, 143.4, 134.3, 133.6, 133.4, 132.9, 132.6, 128.9, 128.8, 128.0, 127.4, 126.9, 60.2, 54.1, 51.0, 28.8, 26.6, 25.9, 19.8, 19.7, 17.9, 11.4. Anal. Calcd. for $C_{34}H_{40}N_{10}O_7$: C, 58.28; H, 5.75; N, 19.99. Found: C, 58.17; H, 5.80; N 19.85.

tert-Butyl (4-(2-((2-((1-(2-(1H-indol-3-yl)ethyl)-2-(methylcarbamoyl)-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl)-1-isobutyl-6-oxo-1,6-dihydropyrimidin-5-yl)carbamoyl)-5-benzamido-6-oxopyri-

midin-1(6H)-yl)butyl)carbamate (**8b**). Yield 41%, 188 mg, yellow solid: R_f = 0.28 (ethyl acetate); mp 243 °C (from ethyl acetate); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.88 (s, 1H), 10.66 (s, 1H), 10.59 (s, 1H), 9.53 (s, 1H), 8.88 (s, 1H), 8.84 (s, 1H), 8.80−8.78 (m, 2H), 7.97−7.95 (m, 2H), 7.73−7.68 (m, 1H), 7.65−7.61 (m, 1H), 7.57−7.53 (m, 2H), 7.35−7.33 (m, 1H), 7.17−7.13 (m, 1H), 7.11−7.09 (m, 1H), 7.03−6.99 (m, 1H), 6.79 (s, 1H), 4.45−4.38 (m, 2H), 4.35−4.26 (m, 4H), 3.16−3.12 (m, 2H), 2.98−2.94 (m, 2H), 2.72 (d, J = 2.9 Hz, 3H), 2.15−2.13 (m, 1H), 1.77−175 (m, 2H), 1.48−1.45 (m, 2H), 1.37 (s, 9H), 0.91 (d, J = 5.5 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.4, 161.2, 159.0, 158.9, 157.2, 157.0, 156.6, 155.5, 148.2, 145.5, 144.8, 144.7, 136.3, 136.0, 135.8, 134.9, 133.1, 132.4, 128.7, 127.6, 127.3, 127.0, 126.4, 125.9, 123.2, 121.1, 118.4, 118.3, 111.5, 110.0, 77.4, 50.9, 46.2, 45.3, 28.2, 28.2, 26.9, 25.9, 25.8, 24.4, 19.8. Anal. Calcd. for $C_{46}H_{52}N_{12}O_9$: C, 60.25; H, 5.72; N, 18.33. Found: C, 59.98; H, 5.72; N 18.35.

Preparation of Unprotected Trimer 8c. The *tert*-butylcarbamate **8b** (0.05 g, 0.054 mmol) was suspended in dichloromethane (2 mL) and cooled with an ice bath. Trifluoroacetic acid (0.5 mL) was added slowly. After 15 min all starting material was dissolved, and the ice bath was removed. The mixture was stirred at room temperature for 3 h and evaporated under a vacuum. Toluol (2 mL) was added, and the mixture was revaporated.

1-(2-(1H-Indol-3-yl)ethyl)-5-(5-(1-(4-aminobutyl)-5-benzamido-6-oxo-1,6-dihydropyrimidine-2-carboxamido)-1-isobutyl-6-oxo-1,6-dihydropyrimidine-2-carboxamido)-N-methyl-6-oxo-1,6-dihydropyrimidine-2-carboxamide trifluoroacetate (**8c·TFA**). Yield 92%, 46 mg, yellow solid: R_f = 0.05 (ethyl acetate); mp 243 °C ; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.85 (s, 1H), 10.60 (s, 1H), 10.54 (s, 1H), 9.51 (s, 1H), 8.82 (s, 1H), 8.79 (s, 1H), 8.74 (s, 2H), 7.90 (d, J = 7.3, 2H), 7.74 (s, 3H), 7.62 (d, J = 7.7, 1H), 7.57 (d, J = 7.1, 1H), 7.50 (d, J = 7.2, 2H), 7.30 (d, J = 7.9, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 7.02 (s, 1H), 6.95 (d, J = 7.3, 1H), 4.32 (d, J = 18.5, 2H), 4.29 (s, 2H), 4.22 (s, 2H), 3.06 (s, 2H), 2.79 (s, 2H), 2.66 (d, J = 4.2, 3H), 2.43 (s, 2H), 2.23 (s, 1H), 2.07 (s, 1H), 1.77 (s, 2H), 1.57 (s, 2H), 0.84 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.5, 161.2, 159.1, 158.9, 157.3, 157.0, 156.7, 148.3, 144.8, 136.3, 136.2, 135.0, 133.1, 132.4, 128.9, 128.7, 128.2, 127.6, 127.3, 127.0, 126.4, 125.9, 123.2, 121.1, 118.4, 118.2, 111.5, 110.0, 51.0, 46.2, 44.8, 38.5, 28.2, 25.8, 25.5, 24.4, 24.3, 19.8; HRMS (EI) m/z calcd. for $C_{41}H_{45}N_{12}O_7$ $[M]^+$ 817.35287, found 817.35302.

The residue was taken up in water (1 mL) and sodium hydroxide solution (15 wt %) was added until pH 9. The resulting suspension was extracted with ethyl acetate (3 × 5 mL). After drying over sodium sulfate, the solvent was removed, and the residue was treated with diethyl ether to crystallize. The solid was collected and washed with ethyl acetate/hexane (1:2) to give the deprotected amine **8c**.

1-(2-(1H-Indol-3-yl)ethyl)-5-(5-(1-(4-aminobutyl)-5-benzamido-6-oxo-1,6-dihydropyrimidine-2-carboxamido)-1-isobutyl-6-oxo-1,6-dihydropyrimidine-2-carboxamido)-N-methyl-6-oxo-1,6-dihydropyrimidine-2-carboxamide (**8c**). Yield 90%, 44 mg, yellow solid: R_f = 0.10 (ethyl acetate); mp 218 °C ; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.89 (s, 1H), 8.86 (s, 1H), 8.83 (s, 1H), 8.80 (s, 1H), 7.98 (d, J = 7.4 Hz, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.57 (t, J = 7.6 Hz, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.16 (s, 1H), 7.09 (t, J = 7.4 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 4.40 (s, 2H), 4.30−4.26 (m, 4H), 3.13 (s, 2H), 2.72 (d, J = 3.8 Hz, 3H), 2.65 (t, J = 7.0 Hz, 2H), 2.13 (s, 1H), 1.80 (d, J = 15.2 Hz, 2H), 1.49 (s, 2H), 0.90 (d, J = 6.6 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.4, 161.3, 159.3, 159.2, 157.2, 157.2, 157.2, 156.7, 148.2, 145.7, 145.6, 136.4, 136.3, 136.2, 135.2, 133.2, 132.4, 128.7, 127.0, 126.1, 123.2, 121.1, 118.4, 118.3, 111.5, 110.0, 50.9, 46.2, 45.3, 40.2, 40.0, 28.3, 28.1, 25.8, 25.7, 24.4, 22.6, 19.8; HRMS (EI) m/z calcd. for $C_{41}H_{45}N_{12}O_7$ $[M]^+$ 817.35287, found 817.35405.

Crystal Structure Determination. Only very thin crystals of limited quality were available in the case of compound **8a**. One was selected by means of a polarization microscope and investigated with a STOE Imaging Plate Diffraction System at 123 K using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å) applying long time exposures. Unit cell parameters were determined by least-squares refinements on the positions of 8000 reflections. Space group type no. 14 was uniquely determined. Corrections for Lorentz and polarization effects were applied. The structure was solved by direct methods[62] and subsequent ΔF-syntheses. In the course of structure refinement, intermolecular coupled disorder was detected with respect to the *sec*-butyl group attached to N5 and the isobutyl group attached to N3 (0.73(1):0.27(1) and 0.28(1):0.72(1)). Approximate positions of all but some of the hydrogen atoms in the disorder region were found in different stages of converging refinements by full-matrix least-squares calculations on F^2.[63] Anisotropic displacement parameters were refined for all atoms heavier than hydrogen with the exception of the atoms of the disordered group including atoms C13 to C16. With idealized bonds lengths and angles assumed for all the CH, CH_2, and CH_3 groups, the riding model was applied for the corresponding H atoms, and their isotropic displacement parameters were constrained to 120, 120, and 150% of the equivalent isotropic displacement parameters of the parent carbon atoms, respectively. In addition the H atoms of the CH_3 groups were allowed to rotate around the neighboring C−C bonds. Idealized bond lengths were also assumed for the NH groups; their orientation was refined, and their isotropic displacement parameters were constrained to 120% of the equivalent isotropic displacement parameters of the parent nitrogen atoms. Appropriate same distance and anisotropic displacement restraints had to be applied for atoms of the disorder region. CCDC-946095 contains the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Modeling Studies. The torsion angles ϕ and ψ (Figure S4A, Supporting Information) are crucial for the conformational properties of the trispyrimidonamide scaffold. Thus, we parametrized the respective torsion angle potentials for use with other parameters of the molecular mechanics general AMBER force field (GAFF).[64] Conformations of a dimethyl substituted bispyrimidonamide (Figure S4A, Supporting Information) were optimized by means of Gaussian 03[65] at the MP2/6-31G* level of theory with the torsion angles ϕ and ψ constrained at intervals of 15° over a range of 360°. Similarly, the conformations were optimized (constrained to the same inter-ring torsion angles) by using the GAFF force field within Amber 11.[66] New molecular mechanics torsion angle potentials for ϕ and ψ were then derived by a fitting procedure carried out with the Amber module Paramfit.[67] Partial charges for di- and trimethyl substituted bis- and trispyrimidonamides (Figure S4A, Supporting Information, and Figure 3A (**IV**) in the main text, respectively) were obtained by RESP fitting to the HF/6-31G* electrostatic potentials of minimum conformations.[68] Minimization, equilibration, and MD simulations of 1.5 μs length of **IV** in explicit solvent were performed with the Amber11 software package using the GAFF force field together with the above derived parameters and standard procedures (TIP3P water, MeOH or $CHCl_3$ model, PBC, PME, SHAKE, time step of 2 fs). The distributions of torsion angles were analyzed with the Amber module *ptraj*.[69]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed description of amide coupling optimization, ^{1}H NMR and ^{13}C NMR spectra for compounds **3**−**8**, X-ray crystallographic data for **8c** (CIF), parametrization of the inter-ring torsion angles ψ and ϕ, and overlay of C_β atoms of a canonical α-helix at positions i, i + 4, and i + 7 onto corresponding methyl groups of **IV**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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