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Design and Synthesis of Urea-Linked Aromatic Oligomers—A Route Towards Convoluted Foldamers

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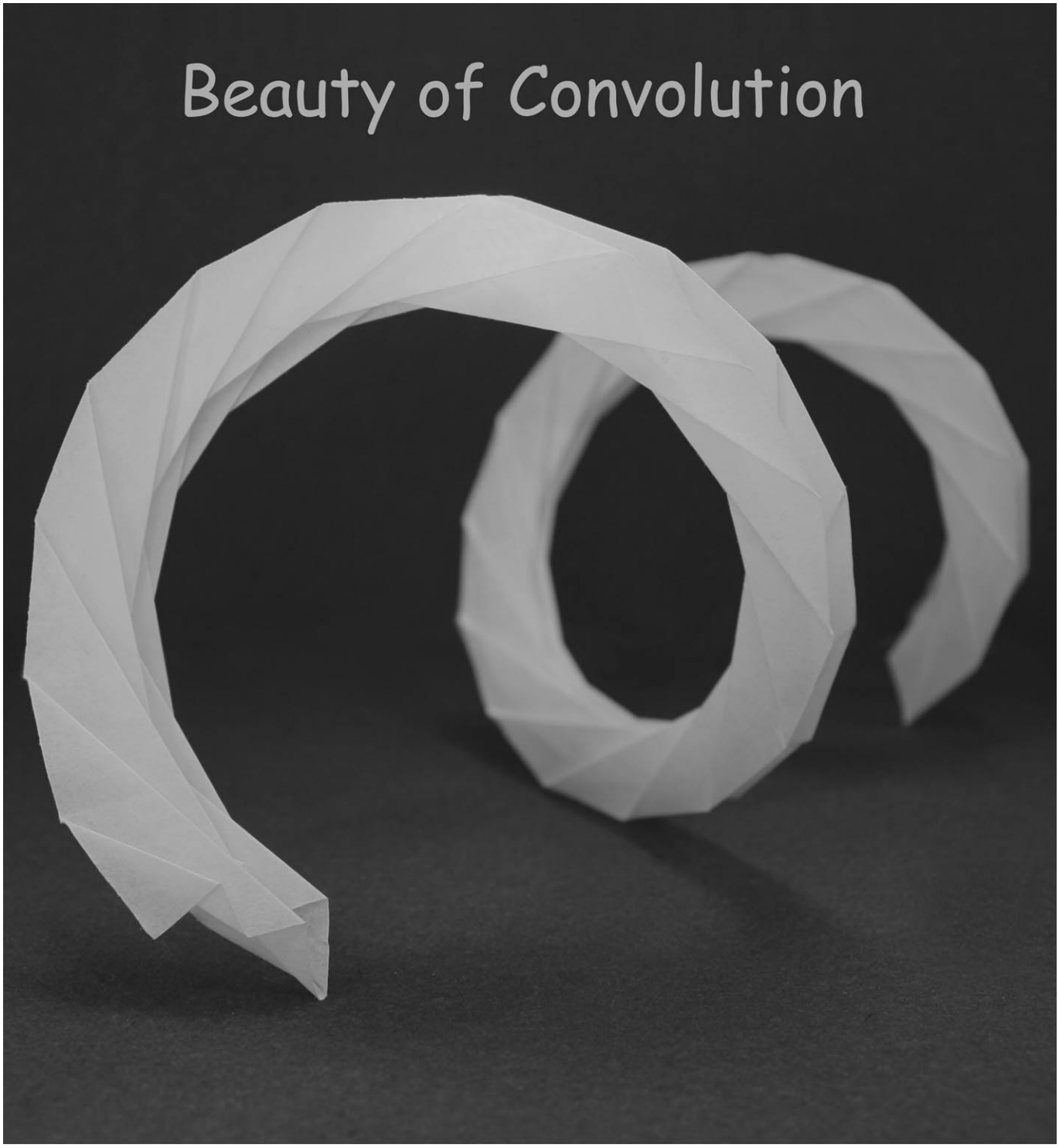

Abstract: Herein we report the design and synthesis of crescent-shaped and helical urea-based foldamers, the curvature of which is controlled by varying the constituent building blocks and their connectivity. These oligomers are comprised of two, three or five alternating aromatic heterocycles (pyridazine, pyrimidine or pyrazine) and methyl-substituted aromatic carbocycles (tolyl, *o*-xylyl or *m*-xylyl) connected together through urea linkages. A crescent-shaped conformational preference is encoded within these π-conjugated urea-linked oligomers based on intramolecular hydrogen bonding and steric interactions; the degree of curvature is tuned by the urea connectivity to the heterocycles and the aryl groups. NMR characterization of these foldamers confirms the intramolecular hydrogen-bonded conformation expected (*Z*,*E* configuration of the urea bond) in both the pyridazyl and pyrimidyl foldamers in solution. An X-ray crystal structure of the N^3,N^6-diisobutylpyridazine-4,6-diamine–*o*-tolyl urea-linked foldamer (**4**) confirms the presence of N−H···N hydrogen bonds between the heterocyclic nitrogen atom and the free hydrogen of the urea linkage. Additionally, the tolyl methyl group interacts unfavourably with the urea carbonyl oxygen, thus destabilising the alternate planar conformation.

Keywords: helical structures · heterocycles · hydrogen bonds · supramolecular chemistry · ureas

Introduction

Complex, well-defined structures found throughout nature are continuously intriguing and inspiring biologists, biochemists and chemists. A recurring theme in most biological macromolecules is the presence of controlled and well-defined intramolecular folding. Consequently, there has been much effort in recent years to prepare synthetic analogues of natural folding molecules to better understand the mechanism of natural folding, which is of vital importance to most protein, polysaccharide and nucleic acid structure–function relationships.[1,2] The term *foldamer*[3,4] was recently redefined by Gellman as "unnatural oligomers that display conformational propensities akin to those of proteins and nucleic acids".[5]

Several families of aromatic crescent or helical foldamers with predictable structures have been studied extensively and include carbocyclic aromatic and heteroaromatic oligoamides,[6–8] aromatic oligohydrazines,[9] aromatic oligohydrazides[10] and directly linked aromatic heterocycles.[11–13] Of specific importance to this research is the aryl−NHCO linkage that encompasses the urea foldamers described herein. Examples of urea-linked foldamers particularly pertinent to this account include: 1) enforced folding and cyclisation of backbone-rigidified aromatic oligoureas of *meta*-linked benzene rings,[14] 2) poly(ureido-*para*-phthalimidyl) foldamers in which the urea N−H groups adopt a *cisoid* conformation,[15] 3) aromatic antibacterial urea oligomers with NH···S interactions on every ring,[16] 4) naphthyridinylurea oligomers that have the potential to exist as an unfolded β-sheet (intermolecular hydrogen bonding) or a folded helical structure (intramolecular hydrogen bonding)[17] and 5) benzoylurea oligomers that mimic extended α-helices.[18]

The research described herein deals with backbone rigidified crescent-shaped foldamers in which local conformational preferences stabilise folded structures and reduce the number of non-folded states to promote well-defined molecular conformations. Specifically, the rotation about all single bonds within the structures is restricted in such a fashion as to greatly favour one conformation over all others. In essence, the goal is to understand *and* control intramolecular non-covalent interactions in relation to the unfavourable entropy associated with self-organisation. This work describes the synthesis and characterisation of molecular building blocks from which foldamers with varying degrees of curvature can be obtained. They are based on the relative orientation between consecutive heterogeneous backbone units as defined by precisely designed non-covalent interactions. For example, directly linked heteroaromatic foldamers comprised of alternating pyridine–pyrazine (*meta–ortho* connectivity),[11] pyridine–pyrimidine (*meta–meta* connectivity)[12] or pyridine–pyridazine (*meta–para* connectivity)[13] rings form helical structures with four, six or twelve heterocycles per helical turn, respectively, due to the preferred *transoid* conformation of inter-heterocyclic bonds. Precise shape control has also been demonstrated in amide-linked carbocyclic aromatic[6] or heteroaromatic[19] foldamers in which the *ortho*, *meta* and/or *para* connectivity in combination with the restricted rotation associated with hydrogen bonding ultimately control the conformation of the building blocks thus the degree of curvature in the final folded structure. Not surprisingly, one can take advantage of crescent-shaped building blocks with varying degrees of curvature to access a wide range of shape-persistent macrocyclic compounds in one or more synthetic steps.[20–24] Clearly, a high degree of preorganisation during synthesis can have a *self-templating* effect to promote intramolecular macrocyclisation under non-high dilution conditions.

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Results and Discussion

We recently described the synthesis of macrocycles bearing urea linkages between alternating pyridazyl and tolyl moieties (e.g., **MC6**; Figure 1).[24] The ease of macrocyclisation

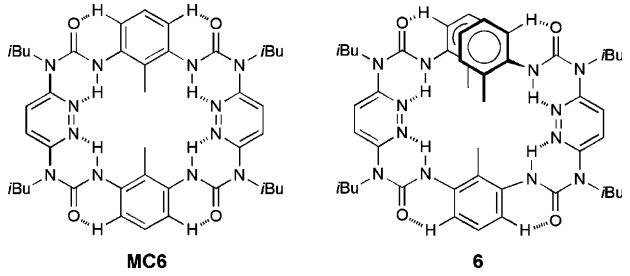


Figure 1. Macrocycle (**MC6**) and foldamer (**6**) bearing urea linkages between alternating pyridazyl and tolyl moieties. Foldamer **6** is shown in its optimal helical conformation with hydrogen bonds represented as hash lines.

was attributed to the high degree of pre-organisation present in the growing molecule and it was envisioned that these same building blocks and interactions could provide access to helical foldamers (e.g. **6**; Figure 1). There are three main interactions working in concert to influence the conformation and folding in this design: 1) N–H···N hydrogen bonds between the heterocyclic nitrogen atom and the free hydrogen of the urea linkage, 2) C–H···O hydrogen bonding interactions between the carbonyl oxygen of the urea linkage and the *ortho* hydrogen atom on the neighbouring non-heterocyclic ring and 3) steric repulsion between the non-aromatic methyl group and the urea carbonyl group. Finally, a favourable slipped stack π–π interaction between overlapping aromatic groups is also possible once one turn of the helix is obtained. These interactions are expected to act in a cooperative fashion to restrict rotation about all single bonds of the urea linkage.

With the foldamer design in place, the next step was to explore possibilities for tuning the curvature of these molecules. It was envisaged that by varying the diazine moeity (pyridazines **1**, pyrimidines **2** and pyrazines **3**; Figure 2) one could influence the degree of curvature by virtue of the substitution pattern of the heterocycle (**1a**, **2a** and **3a**, respectively; Figure 2). Furthermore, varying the non-heterocyclic moiety from tolyl to *o*-xylyl or *m*-xylyl also provides a means of altering the curvature of the repeating motif (**1a**, **1b** and **1c**, respectively; Figure 2). A useful way of looking at this flexible design principle with regards to curvature is to calculate the number of aromatic units needed to form a macrocycle using each motif. For example, motifs **1a**, **1b** and **1c** would form macrocycles with four, twleve and six aromatic units, respectively.

Pyridazyl foldamers were synthesised following the sequence of reactions shown in Scheme 1. N^3,N^6-Diisobutylpyridazine-3,6-diamine (**1**) was prepared as previously described by reacting 3,6-dichloropyridazine with isobutyl amine in a Parr reactor at 155 °C to give the desired product

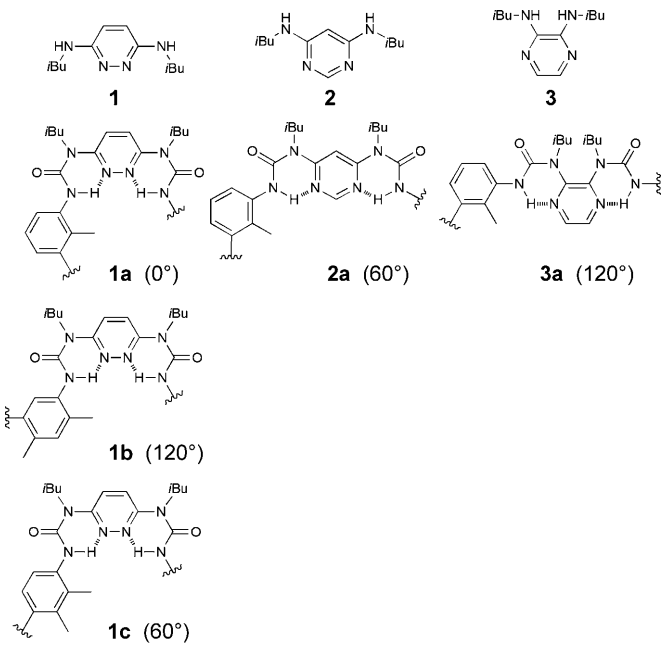
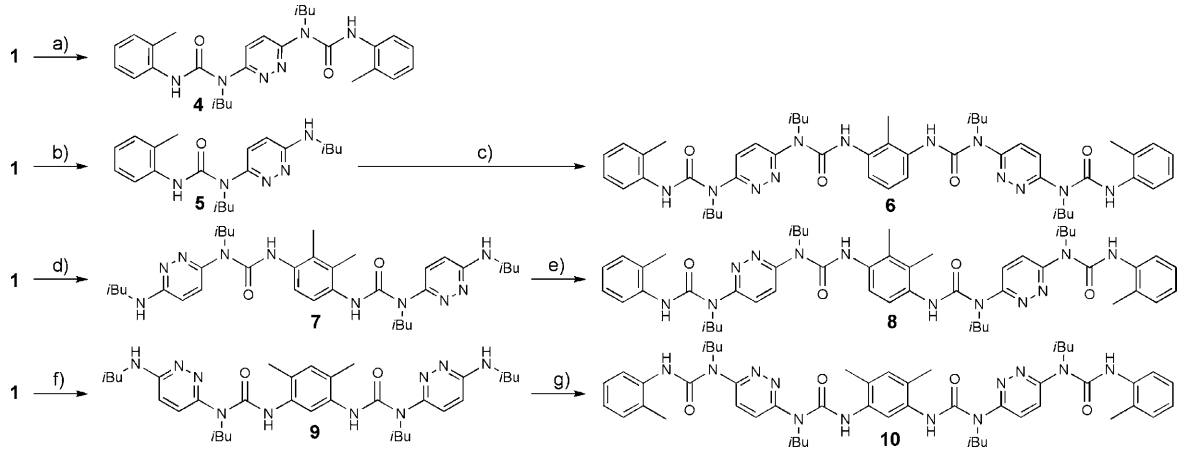


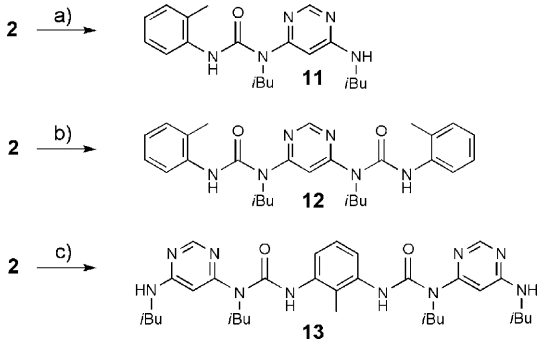
Figure 2. Structure of the heterocyclic core units N^3,N^6-diisobutylpyridazine-4,6-diamine (**1**), N^4,N^6-diisobutylpyrimidine-4,6-diamine (**2**) and N^2,N^3-diisobutylpyrazine-2,3-diamine (**3**). Variations in the heteroaromatic (**1a**, **2a** and **3a**) or carbocyclic aromatic (**1a**, **1b** and **1c**) group of the basic building blocks yield different angles of curvature, between the broken bonds, for the heteroaromatic/urea/carbocyclic aromatic unit. Hydrogen bonds are represented as hash lines.

in 76 % yield. The isobutyl group was chosen to increase solubility of the foldamers and to promote the formation of crystalline products. Compound **4** was prepared in 74 % yield by reacting diamine **1** with excess *o*-tolylene isocyanate. Products, such as **4**, containing tolyl groups at the termini were designated as being *capped* as the chain can no longer be extended. Foldamer **6** was prepared in 39 % yield from the reaction of the half-capped compound **5** with tolylene-2,6-diisocyanate (TDI) in chloroform for 16 h at 40 °C. Products containing the *o*-xylyl moiety (oxyl foldamers) were prepared using a different route. Since the corresponding diisocyanate was not commercially available, the urea linkages were formed using the corresponding biscarbamate. Compound **7** was synthesised from the bisisopropenyl carbamate of 2,3-dimethylbenzene-1,4-diamine.[25,26] Compound **7** was subsequently capped with excess *o*-tolylene isocyanate to give compound **8** in 54 % yield. Pyridazyl oligomers containing the *m*-xylyl monomer (mexyl foldamers) were prepared similarly to the oxyl foldamers. Compound **9** was prepared in one pot using the bis-*p*-nitrophenyl carbamate of 1,5-dimethyl-2,4-phenylenediamine; which was reacted in situ with diamine **1**.[25,27] This was readily converted to compound **10** by capping with *o*-tolylene isocyanate.

Pyrimidyl foldamers were synthesised according to Scheme 2. N^4,N^6-Diisobutylpyrimidine-4,6-diamine (**2**) was prepared similarly to N^3,N^6-diisobutylpyridazine-3,6-diamine (**1**), starting from 4,6-dichloropyrimidine and isobutyl amine. Products **11** and **12** were prepared from diamine **2** and *o*-tolylene isocyanate. However, due to the lower reactivity of di-



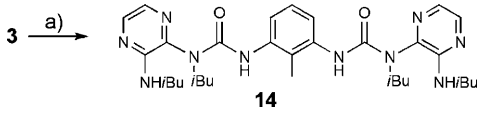
Scheme 1. a) *o*-Tolylene isocyanate (3 equiv), $CHCl_3$, 50 °C, 5 h, 74 %; b) *o*-tolylene isocyanate (1.2 equiv), $CHCl_3$, 50 °C, 5 h, 68 %; c) TDI (0.5 equiv), $CHCl_3$, 24 h, 39 %; d) NaOH (3.5 equiv), **22** (1 equiv), H_2O, EtOAc, isopropenyl chloroformate (2.8 equiv), 3 h, then **8** (1.1 equiv), *N*-methyl pyrolidine (20 mol %), 55 °C, 48 h, 16 % (over 2 steps); e) *o*-tolylene isocyanate (6.4 equiv), $CHCl_3$, 55 °C, 24 h, 54 %; f) 4-nitrophenyl chloroformate (2.5 equiv), CH_2Cl_2, **23** (1 equiv), DIEA (2 equiv), 1 h, then **8** (1.1 equiv) 20 h, RT, 13 % (over 2 steps); g) *o*-tolylene isocyanate (6.4 equiv), $CHCl_3$, 55 °C, 24 h, 51 %.



Scheme 2. a) *o*-Tolylene isocyanate (1 equiv), toluene, 90 °C, 24 h, 73 %; b) *o*-tolylene isocyanate (3 equiv), toluene, 90 °C, 48 h, 75 %; c) TDI (0.45 equiv), toluene, 90 °C, 24 h, 44 %.

amine **2** in comparison to diamine **1**, presumably due to the relative electron deficiency of the pyrimidine heterocycle, the reaction required elevated temperatures to obtain good conversions.[28] Compound **13** was obtained in 44 % yield from the reaction of diamine **2** with TDI. Again, elevated temperatures were required for the reaction to proceed. Attempts to prepare longer pyrimidyl oligomers were unsuccessful. Interestingly, when compound **13** was treated with *o*-tolylene isocyanate, formation of compound **12** was observed. Compound **13** likely degrades to the corresponding TDI and N^4,N^6-diisobutylpyrimidine-4,6-diamine, which then reacts with the excess *o*-tolylene isocyanate present in solution. Attempts to circumvent this reversibility were unsuccessful. The reactions of compound **2** with the same oxyl and mexyl biscarbamates used to prepare compounds **7** and **9** were unsuccessful, again likely due to the decreased nucleophilicity of diamine **2** versus diamine **1**.

N^2,N^3-Diisobutylpyrazine-2,3-diamine (**3**) was obtained from the reaction of isobutyl amine with 2,3-dichloropyrazine. This diamino heterocycle was the least reactive of the three diazines. The reaction of diamine **3** with *o*-tolylene isocyanate was unsuccessful; however, compound **14** was prepared in 21 % yield from the reaction of **3** with TDI (Scheme 3). The rational for the poor yield is the high degree of steric strain in the system as a result of the *ortho* substitution of the pyrazine heterocycle.



Scheme 3. a) TDI (0.5 equiv), toluene, 90 °C, 24 h, 21 %.

Folding in pyridazyl foldamers: The designed pre-organisation was observed with the crescent-shaped, capped foldamer **4**. This was determined through proton NMR spectroscopy as the chemical shift of the urea proton was observed at $\delta = 11.57$ ppm in comparison to non-hydrogen bonded heterocyclic urea protons at $\delta \approx 10.6$ ppm.[24] This degree of deshielding is also characteristic of hydrogen-bonded amide-based foldamers.[7] Additionally, the proton at the 6-position of the tolyl group was shifted to $\delta = 7.97$ ppm, compared to $\delta = 7.13$ ppm in *o*-tolylene isocyanate, suggesting that hydrogen bonding with the urea carbonyl oxygen is also present (Figure 3). NOESY analysis detected an NOE cross peak between the urea proton and the tolyl methyl group, a consequence of hydrogen-bond restricted rotation about the linking urea bonds and the unfavourable steric interaction between the tolyl methyl group and the urea carbonyl group (Figure 1).[29] This preferred *Z*,*E* configuration of the urea bond was confirmed from the X-ray structure of foldamer **4** (Figure 4).[30] The N–H···N distance was measured at a reasonable hydrogen-bond distance of 1.91 Å. There is also evidence for molecular helicity as the two terminal tolyl groups display a slight twisting out of plane due to weak van der Waals repulsion between the two tolyl methyl groups.

Evidence for similar N–H···N hydrogen bonding interactions was observed in compound **6**, in which the urea pro-

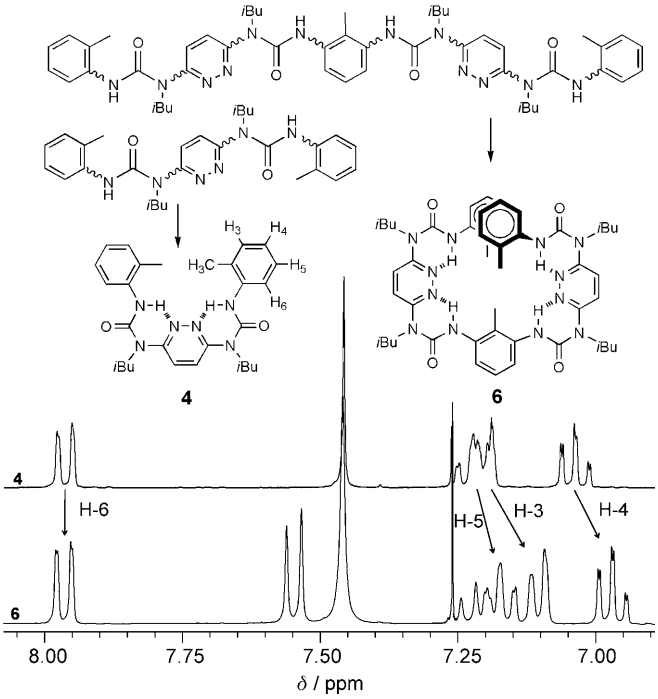


Figure 3. ^{1}H NMR spectra of compounds **4** and **6** from $\delta = 6.9$ to 8.1 ppm. The chemical shifts due to π–π stacking in H-3, H-4 and H-5 are highlighted with arrows.

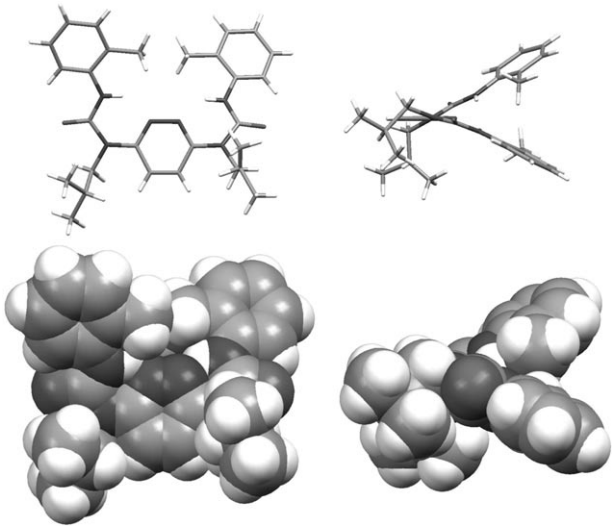


Figure 4. X-ray crystal structure of foldamer **4**—front and side view (left and right); stick and space-filling representation (upper and lower). For clarity only the *M*-helix is shown.

tons were present at $\delta = 11.58$ and 11.44 ppm (Figure 5). Compound **6** is expected to give a full helical turn with the terminal tolyl groups in a slipped π-stacking arrangement. This stacking was confirmed by ^{1}H NMR spectroscopy for which the terminal tolyl protons are more shielded than those of compound **4** due to ring anisotropy in the helical conformation (Figure 3).

As expected, both compounds **7** and **9** displayed similar NMR signatures as those observed for compound **4**. The urea proton signals occurred at $\delta = 10.25$ and 10.15 ppm for **7** and **9**, respectively, indicative of the expected N–H···N hydrogen bonding. Additionally, 2D NOESY analysis of compounds **7** and **9** showed the same NOE effect between the urea proton and the xylyl methyl groups, suggesting that the same urea *Z*,*E* configuration was present, again due to restricted rotation about the urea bonds and steric interactions between the carbonyl oxygen and the tolyl methyl groups.[29] The oxyl C–H···O protons at the 5- and 6-positions in compound **7** exhibited a chemical shift at $\delta =$ 7.48 ppm while the mexyl proton at the 6-position in compound **9** was at $\delta = 8.15$ ppm. Protons H-5 and H-6 of the oxyl group each hydrogen bond to one carbonyl oxygen on either side of the ring, while both carbonyl oxygen atoms can hydrogen bond with a single proton at the 6-position in the mexyl group. Encouraged by the consistency of the fold-

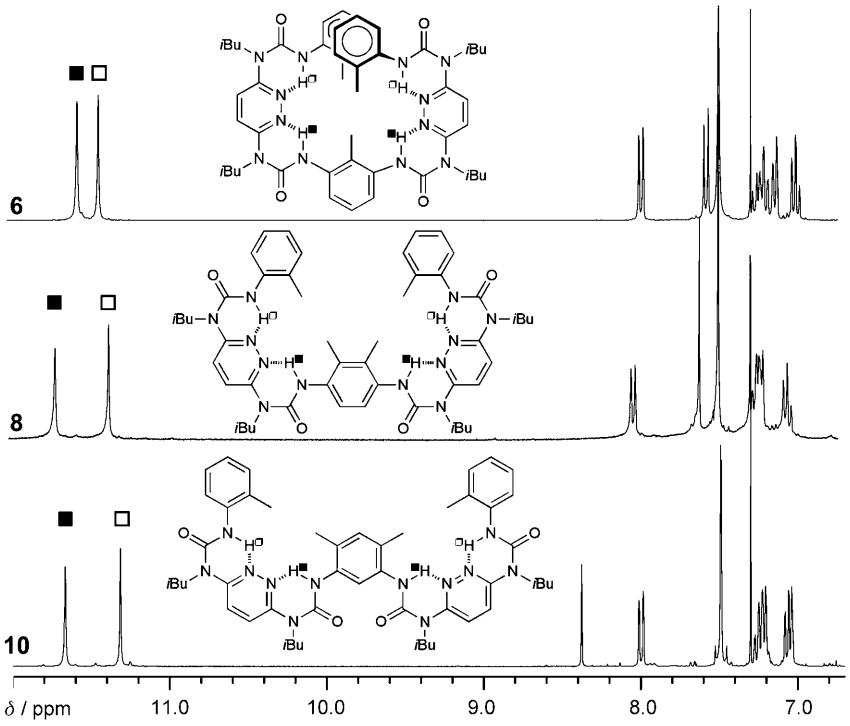


Figure 5. ^{1}H NMR spectra of compounds **6**, **8** and **10** from $\delta = 7$ to 12 ppm. The N–H···N hydrogen bonded protons are highlighted with black and white squares.

ing properties observed thus far, longer oxyl and mexyl foldamers were synthesised. A comparison of the ^{1}H NMR spectra of foldamers **6**, **8** and **10** shows that similar folding patterns are present in all three systems (Figure 5). Though the xylyl pentamers do not complete a full helical turn, the same hydrogen bond-induced chemical shifts and NOESY analysis confirm their folding.[29] Most importantly, due to the difference in the linking of the tolyl, oxyl and mexyl oligomers, three unique curvatures were obtained allowing for fine control of the overall shape in the final foldamers.

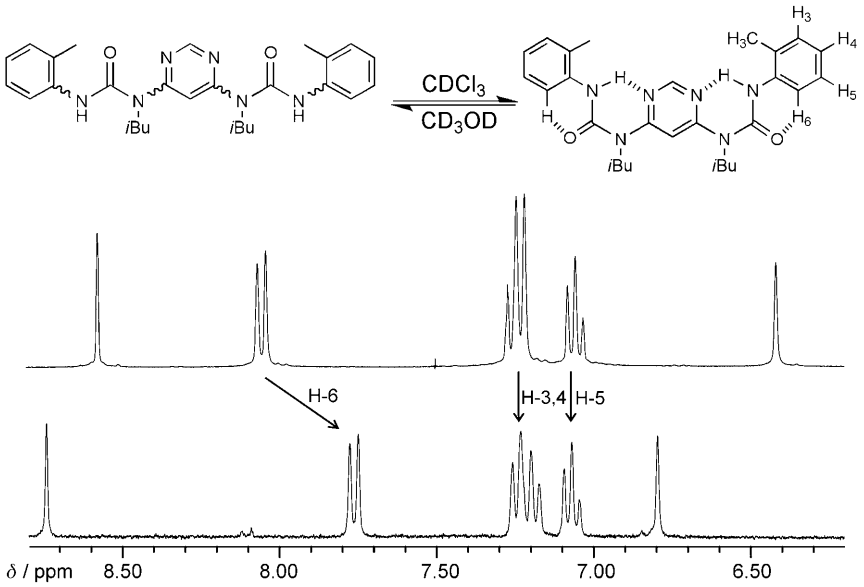


Figure 6. ^{1}H NMR spectrum of the tolyl proton region of compound **12** in [D]chloroform (upper) and [D_4]methanol (lower). The chemical shift of H_6 is highlighted with an arrow.

Folding in pyrimidyl foldamers: Similar to pyridazyl compound **5**, pyrimidyl compound **11** also displayed a level of preorganisation due to hydrogen bonding as indicated by the relatively downfield location of the urea proton. This was also observed in the capped compound **12** and the uncapped compound **13**, for which the chemical shifts of the urea protons were observed at $\delta = 12.55$ and 12.80 ppm, respectively. As with the pyridazyl foldamers, NOESY analysis of compound **12** displayed an NOE cross peak between the urea protons and the tolyl methyl group, again demonstrating the *transoid* relationship between the carbonyl oxygen and the tolyl methyl group.[29] However, unlike the pyridazyl foldamers, the presence of a proton at the 2-position of the pyrimidine ring should yield a NOE cross peak with the tolyl methyl group as the distance was estimated to be approximately 2.6 Å. Indeed, a cross peak was observed, confirming the expected folding motif of compound **12**. As observed for the pyridazyl foldamers, this folding was assisted by the presence of C–H···O hydrogen bonds as protons at the 6-position of the tolyl group were detected at $\delta = 8.05$ and 8.28 ppm for compounds **12** and **13**, respectively. In order to confirm the importance of hydrogen bonding for folding a ^{1}H NMR spectrum of compound **12** was obtained in neat [D_4]methanol. As expected, the urea proton underwent complete deuterium exchange. Additionally, H-6 of the tolyl ring was shifted upfield from $\delta = 8.05$ to 7.75 ppm. This is believed to be the result of a solvent induced disruption of intramolecular hydrogen bonding, since the remaining tolyl chemical shifts were unchanged (Figure 6). Perhaps the most poignant example of this conformational disruption was observed through the NOESY spectra of compounds **12** and **13**, in which the NOE cross peak between H-2 of the pyrimidine ring and the tolyl methyl protons disappeared, suggesting that these groups are now too far apart to observe the NOE effect.[29] Under conditions that disrupt hydrogen bonding the oligomer no longer adopts its designed folded conformation.

Folding in pyrazyl foldamers: The pyrazyl oligomer **14** exhibited markedly different conformational properties as compared to the corresponding pyridazyl and pyrimidyl compounds (**9** and **13**, respectively). Whereas in the last two cases, the urea proton chemical shifts were greater than $\delta =$ 10 ppm, the pyrazine urea proton signal of compound **14** was observed only at 6.93 ppm, suggesting that hydrogen bonding does not occur, and thus the oligomer is not folding as designed. This was further confirmed through NOESY experiments in which the expected cross peak between H-6 of the pyrazyl group and the methyl protons of the tolyl group was not observed.[29] A possible explanation for this is due again to steric strain of the system. The unfavourable steric interaction between the isobutyl chains attached at the *ortho*-position of the heterocycle with the carbonyl group of the urea linkage likely induces a rotation of the C–N urea bonds, increasing the distance between the urea proton and the heterocyclic nitrogen atom. This increased distance can thereby prevent hydrogen bonding, thus allowing for alternate conformations for the oligomer.

Conclusion

The synthesis and characterisation of alternating aromatic heterocycles and methyl-substituted aromatic carbocycles connected together through urea linkages was described. Particularly attractive in this system is the ability to control molecular curvature by varying the constituent building blocks and their connectivity. In the case of the pyridazyl and pyrimidyl urea-linked foldamers, the intended folding

patterns were supported by NMR and X-ray crystallographic data. However, the desired hydrogen bonding was not observed in the case of the pyrazyl molecule, likely as a result of steric strain. The main limitations encountered in the work described herein was the often poor reactivity of heterocyclic amines in the formation of urea linkages and/or steric factors which are detrimental in the formation of longer foldamers.[31] Overall, this system represents an implementation of a basic structural design principle for enforcing controlled and flexible folding in macromolecular systems. Clearly, foldamers continue to be valuable model systems for understanding how natural systems such as proteins, nucleic acids and oligosaccharides undergo their complex folding.

Experimental Section

General: All reagents were obtained from Aldrich and were used without further purification unless specified otherwise. All solvents used were HPLC grade. Dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) and chloroform used in reactions were obtained anhydrous in SureSeal bottles and used under nitrogen flow. [D]Chloroform ($CDCl_3$, 99.8%) and [D_6]DMSO (99.8%) were purchased from Cambridge Isotopes. Melting points (m.p.) were recorded with a capillary melting point apparatus (Thomas Hoover) and are uncorrected. The recorded R_f values were determined by a standard thin-layer chromatography (TLC) procedure: 0.25 mm silica gel plates (Aldrich, Z122785-25EA) eluted with the specified solvents. FTIR spectra were recorded with a Magna-IR spectrometer 550 (Nicolet) in KBr pellets. 300 MHz ^{1}H NMR spectra and 75 MHz ^{13}C NMR spectra were recorded on a Varian 300 spectrometer. MALDI-TOF mass spectra were obtained using a Micromass BAA037 (Micromass, UK) time-of-flight mass spectrometer. A nitrogen laser (337 nm wavelength) was used to desorb the sample ions. The matrices used were dihydroxybenzoic acid (DHB), dithranol (DIT), or *trans*-indoacrylic acid (IAA) and the spectra were recorded in the positive reflectron mode. FAB mass spectra (8 KV, Xe) were recorded on a KRATOS MS25RFA with *m*NBA (*meta*-nitrobenzyl alcohol) as matrix. ESI spectra were recorded on a FINNIGAN LCQ DUO mass spectrometer using an ESI probe by infusion (10 μL min^{-1}) with an integrated syringe pump. X-ray diffraction data was collected on a Bruker D8 X-ray diffractometer with a graphite-monochromatised $Mo_{K\alpha}$ radiation (0.71073 Å), θ scans at 100(2) K.

N^3,N^6-Diisobutylpyridazine-4,6-diamine (1): 3,6-Dichloropyrazine (10 g, 67.1 mmol) and isobutyl amine (30 mL, 302 mmol) were placed in a Parr reactor. The solution was stirred at 155 °C for five days. The dark brown solid obtained was dissolved in chloroform and washed with $NaHCO_3$ (2×25 mL) and distilled water (2×25 mL). The mixture was then concentrated and purified by column chromatography (chloroform/methanol/acetone, 8.5:1.0:0.5) to give the desired product in 76% yield (10.78 g). R_f=0.48 (chloroform/methanol/acetone, 8.5:1.0:0.5); m.p.=141.4–142.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=6.66 (s, 2H; CH), 4.50 (brs, 2H; NH), 3.16–3.14 (m, 4H; CH_2), 1.80–1.95 (m, 2H; CH), 0.96 ppm (d, ^3J=6.3 Hz, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=134.5, 118.0, 50.4, 28.3, 20.4 ppm; IR (KBr): $\tilde{\nu}$=3437, 3021, 2916, 1566, 1501, 1485, 1215 cm^{-1}; MALDI-TOF: *m*/*z* calcd: 223.18; found: 223.25 $[M+H]^+$.

N^4,N^6-Diisobutylpyrimidine-4,6-diamine (2): 4,6-Dichloropyrimidine (6.48 g, 43.4 mmol) and isobutyl amine (25.9 mL, 260 mmol) were place in a tube that subsequently sealed. The solution was heated at 160 °C for three days after which a precipitate formed. The crude reaction mixture was recrystallised from 99% ethanol to obtain a white crystalline solid in 64% yield (5.67 g). R_f=0.95 (chloroform/acetone, 8:2); m.p.=188–189 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=8.05 (s, 1H; CH), 5.21 (s, 1H; CH), 4.83 (brs, 2H; NH), 3.02 (t, ^3J=6.7 Hz, 4H; CH_2), 1.91–1.70 (m, 2H; CH), 0.99 ppm (d, ^3J=6.7 Hz, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=163.2, 157.9, 79.3, 49.5, 28.4, 20.5 ppm; IR (KBr): $\tilde{\nu}$=3431, 2962, 2875, 1603, 1528, 1471, 1248 cm^{-1}; MALDI-TOF: *m*/*z* calcd: 223.18; found: 223.09 $[M+H]^+$; elemental analysis calcd (%) for $C_{12}H_{22}N_4$: C 64.83, H 9.97, N 25.20; found: C 64.84, H 9.65, N 25.08.

N^2,N^3-Diisobutylpyrazine-2,3-diamine (3): 2,3-Dichloropyrazine (2.5 g, 16.8 mmol) and isobutyl amine (7 mL, 70.4 mmol) were placed in a Parr reactor. The solution was stirred at 170 °C for 16 h after which a precipitate formed. The crude product was dissolved in chloroform and washed with saturated $NaHCO_3$ (2×50 mL) and water (2×50 mL). The solvent was concentrated to 5 mL and the mixture was then purified by column chromatography (chloroform/acetone, 9:1) to yield a brown solid in 79% yield (2.95 g). R_f=0.56 (chloroform/acetone, 9:1); m.p.=88–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.46 (s, 2H; CH), 3.96 (brs, 2H; NH), 3.29–3.23 (m, 4H; CH_2), 2.05–1.90 (m, 2H; CH), 1.01 ppm (d, ^3J=6.7 Hz, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=144.9, 129.7, 49.2, 28.0, 20.5 ppm; IR (KBr): $\tilde{\nu}$=3426, 3020, 2962, 2872, 1600, 1550, 1504, 1223 cm^{-1}; MALDI-TOF: *m*/*z* calcd: 222.18; found: 222.79 $[M]^+$; elemental analysis calcd (%) for $C_{12}H_{22}N_4$: C 64.83, H 9.97, N 25.20; found: C 64.55, H 9.72, N 24.9.

N^3,N^6-Diisobutylpyridazine-4,6-diamine–*o*-tolyl urea-linked "trimer" (4): *o*-Tolylene isocyanate (0.39 g, 2.9 mmol) was added through a syringe to a solution of N^3,N^6-Diisobutylpyridazine-4,6-diamine **1** (0.22 g, 0.97 mmol) in anhydrous chloroform (4 mL). The resulting light brown solution was stirred at 50 °C under nitrogen for 5 h. When the reaction was complete by TLC, methanol (5 mL) was added and product mixture was stirred overnight at room temperature to react with the excess of *o*-tolylene isocyanate. Solvent was removed under vacuum and the crude product was redissolved in chloroform (10 mL) and filtered. The filtrate was concentrated to half the volume and then separated by silica gel column chromatography (chloroform/acetone, 9:1) to yield the product as a white wax in 74% yield (0.36 g). Single crystals suitable for X-ray diffraction were obtained by slow evaporation of an ethanol solution. R_f=0.63 (chloroform/ethyl acetate, 9:1); m.p.=130–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=11.57 (s, 2H; NH), 8.05–7.97 (m, 2H; CH) 7.47 (s, 2H; CH), 7.20–7.26 (m, 4H, CH), 7.10–7.04 (m, 2H; CH), 3.98 (d, ^3J=6.9 Hz, 4H; CH_2), 2.39 (s, 6H; CH_3), 2.02–1.80 (m, 2H, CH), 1.01 ppm (d, ^3J=6.6 Hz, 12H; CH_3); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ=154.5, 153.5, 137.3, 130.4, 128.7, 126.7, 124.1, 122.3, 121.9, 51.5, 27.7, 20.1, 18.8 ppm; IR (KBr): $\tilde{\nu}$=2960, 2864, 1676, 1591, 1550, 1460, 1446, 1213 cm^{-1}; ESI: *m*/*z* calcd: 489.29; found: 489.2 $[M+H]^+$, 511.1 $[M+Na]^+$ 998.9 $[2M+Na]^+$.

N^3,N^6-Diisobutylpyridazine-4,6-diamine–*o*-tolyl urea-linked "dimer" (5): Compound **1** (0.50 g, 2.25 mmol) was placed in a round bottom flask and dissolved in anhydrous chloroform (10 mL). The flask was fitted with a nitrogen filled balloon and heated to 50 °C. *O*-Tolyl isocyanate (0.28 mL, 2.25 mmol) was added dropwise through a syringe and the solution was left to stir for 16 h. Methanol (5 mL) was added to quench any unreacted isocyanate and the chloroform was evaporated under vacuum. The solid was redissolved in chloroform and insoluble material was filtered. The filtrate was concentrated to half its volume and the product was purified by silica gel column chromatography (chloroform/acetone, 9:1) to give a pale yellow solid in 56% yield (0.47 g). R_f=0.6 (chloroform, acetone 9:1); m.p.=89–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=10.60 (s, 1H; NH), 7.82 (d, ^3J=7.5 Hz, 1H; CH), 7.10–7.13 (m, 2H; CH), 7.07 (d, ^3J=9.3 Hz, 1H; CH), 6.95 (t, ^3J=7.5 Hz, 1H; CH), 6.73 (d, ^3J=9.3 Hz, 1H; CH), 5.30–5.23 (m, 1H; NH), 3.79 (d, ^3J=6.9 Hz, 2H; CH_2), 3.28–3.17 (m, 2H; CH_2), 2.27 (s, 3H; CH_3), 2.00–1.87 (m, 2H, CH), 0.95 (d, ^3J=6.3 Hz, 6H; CH_3), 0.91 ppm (d, ^3J=6.3 Hz, 6H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=156.8, 154.3, 151.7, 137.4, 130.2, 129.3, 126.4, 123.7, 122.5, 122.4, 117.4, 52.1, 49.6, 28.2, 27.7, 20.3, 19.9, 18.4 ppm; ESI: *m*/*z* calcd: 356.24; found: 356.3 $[M+H]^+$, 378.2 $[M+Na]^+$, 733.1 $[2M+Na]^+$.

N^3,N^6-Diisobutylpyridazine-4,6-diamine–*o*-tolyl urea-linked "pentamer" (6): Tolylene-2,6-diisocyanate (0.13 g, 0.72 mmol) was added dropwise through a syringe over a period of 4 h under nitrogen to a solution of monocapped dimer **5** (0.51 g, 1.45 mmol) in anhydrous chloroform (2 mL) at 40 °C, . The reaction was allowed to stir for another 20 h. Then

methanol (2 mL) was added and the product mixture was stirred at room temperature for 4 h to remove DIT and its isocyanate derivatives formed during the reaction. The solvent was removed under vacuum and the solid residue was redissolved in chloroform (10 mL) and filtered. The filtrate was concentrated to half the volume and purified by silica gel column chromatography (chloroform/acetone, 8:2) to yield a light yellow product in 39% yield (0.25 g). $R_f = 0.7$ (chloroform/acetone, 8:2); m.p. = 120–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 11.58$ (s, 2H; NH), 11.44 (s, 2H; NH), 7.98 (d, $^3J = 7.8$ Hz, 2H; CH), 7.56 (d, $J = 8.1$ Hz, 2H; CH), 7.47 (br s, 4H; CH), 7.23 (t, $^3J = 8.1$ Hz, 1H; CH), 7.18 (t, $^3J = 7.8$ Hz, 2H; CH), 7.12–7.00 (m, 2H; CH), 6.98 (t, $^3J = 7.5$ Hz, 2H; CH), 4.03–3.97 (m, 8H; CH_2), 2.35 (s, 3H; CH_3), 2.34 (s, 6H; CH_3), 2.05–1.90 (m, 4H; CH), 1.00 (d, $^3J = 2.4$ Hz, 12H; CH_3), 0.99 ppm (d, $^3J = 6.6$ Hz, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 154.5$, 153.9, 153.4, 137.4, 137.3, 130.3, 128.5, 126.7, 126.4, 124.1, 123.9, 122.0, 121.9, 120.8, 51.6, 51.5, 27.7, 20.1, 18.8, 13.6 ppm; ESI: m/z calcd: 885.52; found: 885.5 $[M+H]^+$, 907.4 $[M+Na]^+$, 923.4 $[M+K]^+$.

N^3,N^6-Diisobutylpyridazine-4,6-diamine–*o*-xylyl urea-linked "trimer" (7): NaOH (0.12 g, 3.00 mmol) was dissolved in water (1 mL) in a round-bottomed flask and cooled on ice. 2,3-Dimethylbenzene-1,4-diamine (0.12 g, 0.87 mmol) was dissolved in ethyl acetate (2 mL) and added to the NaOH solution. The mixture was stirred for 10 min on ice after which isopropenyl chloroformate (0.270 mL, 2.40 mmol) was added dropwise. After stirring for 45 min at 0 °C, the flask was removed from the ice and stirred at room temperature for 3 h. The mixture was then diluted in ethyl acetate (20 mL) and washed with saturated NaCl solution (2 × 50 mL) then distilled water (2 × 50 mL). The ethyl acetate was evaporated and the beige biscarbamate was triturated with cold heptane. The *o*-xylyl bisisopropenyl carbamate was next added to a round-bottomed flask with compound **1** (0.22 g, 1.00 mmol) and the flask was purged with nitrogen and fitted with a nitrogen filled balloon. Anhydrous THF (1 mL) was added, the resulting solution was heated to 55 °C and *N*-methyl pyrolidine (0.020 mL, 0.2 mmol) was added dropwise. The mixture was stirred at 55 °C for 48 h. The product was then purified by silica gel column chromatography, first with silica (chloroform/acetone, 8:2), then with alumina (methylelene chloride/ethyl acetate, 9:1) to yield a cream-coloured solid in 16% yield (0.088 g). $R_f = 0.3$ (chloroform/acetone, 8:2); m.p. = 140–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 10.25$ (s, 2H; NH), 7.48 (s, 2H; CH), 7.14 (d, $^3J = 9.6$ Hz, 2H; CH), 6.62 (d, $^3J = 9.6$ Hz, 2H; CH), 4.99 (br t, $^3J = 4.2$ Hz, 2H; CH_2), 3.81 (d, $^3J = 7.49$ Hz, 4H; CH_2), 3.21 (t, $^3J = 6.7$, 4H; CH_2), 2.13 (s, 6H; CH_3), 1.83–1.99 (m, 4H; CH), 1.00 (d, $^3J = 6.7$ Hz, 12H; CH_3), 0.92 ppm (d, $^3J = 6.6$ Hz, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 156.6$, 154.6, 152.0, 133.6, 130.2, 122.8, 121.9, 116.8, 52.2, 49.7, 28.2, 27.7, 20.3, 19.9, 14.9 ppm; IR (KBr): $\tilde{\nu} = 3443$, 3020, 2963, 1666, 1494, 1464, 1260 cm^{-1}; MALDI-TOF: m/z calcd: 633.43; found: 633.50 $[M+H]^+$.

N^3,N^6-Diisobutylpyridazine-4,6-diamine–*o*-xylyl urea-linked "pentamer" (8): Crude compound **7** (0.13 g; 0.068 g, 0.11 mmol calculated from ^{1}H NMR spectroscopy) was dissolved in anhydrous chloroform (3 mL) under a nitrogen atmosphere. *o*-Tolyl isocyanate (0.080 mL, 0.70 mmol) was added dropwise and the reaction mixture was stirred at 55 °C for 24 h. After cooling to room temperature, methanol (5 mL) was added and the mixture was stirred for 4 h. The solvent was concentrated to 2 mL and purified by column chromatography (chloroform/acetone, 9:1) to give a cream-coloured solid in 54% yield (0.053 g). $R_f = 0.7$ (chloroform/acetone, 9:1); m.p. = 117–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 11.71$ (s, 2H; NH), 11.37 (s, 2H; NH), 8.02 (d, $^3J = 8.1$ Hz, 2H; CH), 7.59 (s, 1H; CH), 7.47 (s, 4H; CH), 7.17–7.26 (m, 4H; CH), 7.03 (t, $J = 7.0$ Hz, 2H; CH), 3.98 (d, $^3J = 7.5$ Hz, 8H; CH_2), 2.38 (s, 6H; CH_3), 2.31 (s, 6H; CH_3), 1.92–2.09 (m, 4H; CH), 1.00 ppm (d, $^3J = 6.6$ Hz, 24H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 154.6$, 154.5, 154.1, 153.5, 137.5, 133.8, 130.5, 130.0, 128.6, 126.9, 124.1, 122.3, 122.1, 121.9, 121.8, 51.7, 51.5, 27.8, 20.2, 19.0, 15.5 ppm; IR (KBr): $\tilde{\nu} = 3027$, 2964, 1679, 1541, 1449, 1210 cm^{-1}; MALDI-TOF: m/z calcd: 899.53; found: 899.62 $[M+H]^+$.

N^3,N^6-diisobutylpyridazine-4,6-diamine–*m*-xylyl urea-linked "trimer" (9): 4-Nitrophenyl chloroformate (0.57 g, 2.8 mmol) was added to a round bottom flask and purged with nitrogen. The flask was fitted with a nitrogen filled balloon and anhydrous methylene chloride (4 mL) was added to give a suspension. 1,5-Dimethyl-2,4-phenylenediamine (0.153 g, 1.1 mmol) and DIEA (0.40 mL, 2.2 mmol) in anhydrous methylene chloride (4 mL) was added dropwise yielding an orange solution. The solution was left to stir at room temperature for 1 h. A solution of compound **1** (0.43 g, 1.9 mmol) with triethyl amine (0.30 mL) dissolved in methylene chloride (1 mL) was added dropwise. The solution was left to stir for 20 h and the reaction was monitored using TLC. The solution was left to stir for an additional 4 d with no apparent change shown on TLC. The solvent was evaporated and the yellow solid was dissolved in chloroform and filtered to remove insoluble material. The filtrate was washed with distilled water concentrated and purified by column chromatography (chloroform/acetone, 0.77:0.23) to give a white solid in 13% yield (0.080 g). $R_f = 0.5$ (chloroform/acetone, 0.77:0.20); m.p. = 187–190 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 10.15$ (s, 2H; NH), 8.15 (s, 1H; CH), 7.11 (d, $^3J = 9.8$ Hz, 2H, CH), 6.91 (s, 1H, CH), 6.76 (d, $^3J = 9.8$ Hz, 2H; CH), 5.03 (br t, $^3J = 5.5$ Hz, 2H; NH), 3.78 (d, $^3J = 7.3$ Hz, 4H; CH_2), 3.18 (t, $^3J = 6.4$ Hz, 4H; CH_2), 2.19 (s, 6H; CH_3), 2.05–1.89 (m, 4H; CH), 0.99 (d, $^3J = 6.7$ Hz, 12H; CH_3), 0.89 ppm (d, $^3J = 6.7$ Hz, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 156.7$, 154.1, 152.1, 135.1, 131.6, 125.6, 123.0, 117.7, 116.3, 52.3, 49.8, 28.2, 27.7, 20.3, 20.0, 17.7 ppm; IR (KBr): $\tilde{\nu} = 3444$, 3019, 2970, 1675, 1593, 1523, 1426, 1210 cm^{-1}; MALDI-TOF: m/z calcd: 633.43; found: 633.52 $[M+H]^+$; elemental analysis calcd (%) for $C_{34}H_{52}N_{10}O_2$: C 64.53, H 8.28, N 22.13; found: C 63.40, H 7.04, N 20.94.

N^3,N^6-Diisobutylpyridazine-4,6-diamine–*m*-xylyl urea-linked "pentamer" (10): Crude compound **9** (0.13 g; 0.074 g, 0.12 mmol determined by ^{1}H NMR spectroscopy) was dissolved in anhydrous chloroform (3 mL) under a nitrogen atmosphere. *o*-Tolyl isocyanate (0.080 mL, 0.7 mmol) was added dropwise and the reaction mixture was stirred at 55 °C for 24 h. After cooling, methanol (5 mL) was added and the mixture was stirred for 4 h. The solvent was concentrated to 2 mL and purified by column chromatography (chloroform/acetone, 9:1) to give a white solid in 51% yield (0.055 g). $R_f = 0.7$ (chloroform/acetone, 9:1); m.p. = 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 11.64$ (s, 2H; NH), 11.28 (s, 2H; NH), 8.35 (s, 1H; CH), 7.97 (d, $J = 6.6$ Hz, 2H, CH), 7.44–7.46 (m, 4H; CH), 7.16–7.26 (m, 4H; CH), 6.99–7.06 (m, 3H; CH), 3.96 (d, $^3J = 7.4$ Hz, 8H; CH_2), 2.37 (s, 6H; CH_3), 2.29 (s, 6H; CH_3), 1.89–2.05 (m, 4H; CH), 0.96–1.00 ppm (m, 24H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 154.6$, 154.5, 153.7, 153.6, 137.4, 135.3, 132.0, 130.5, 128.9, 126.8, 125.8, 124.2, 122.4, 122.2, 121.8, 117.9, 51.6, 51.6, 27.8, 20.2, 18.9, 18.2 ppm; IR (KBr): $\tilde{\nu} = 3007$, 2965, 1679, 1541, 1459, 1210 cm^{-1}; MALDI-TOF: m/z calcd: 899.53; found: 899.49 $[M+H]^+$.

N^4,N^6-Diisobutylpyrimidine-4,6-diamine–tolyl urea-linked "dimer" (11): Compound **2** (0.50 g, 2.25 mmol) was placed in a flame-dried flask along with a stir bar. The flask was purged with nitrogen and fitted with a nitrogen filled balloon, after which anhydrous toluene (10 mL) was added. *o*-Tolyl isocyanate (0.28 mL, 2.25 mmol) was added dropwise and the solution was stirred at 90 °C for 24 h. The solution was allowed to cool and methanol (5 mL) was added to quench any remaining isocyanate. The solvent was evaporated and chloroform (10 mL) was added to the resulting white solid. The mixture was filtered to remove insoluble material, and the filtrate was purified by column chromatography (methylelene chloride/ethyl acetate, 9.5:0.5) to yield a white solid in 73% yield (0.583 g). $R_f = 0.33$ (methylelene chloride/ethyl acetate, 9.5:0.5); m.p.: 110–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 12.93$ (s, 1H; NH), 8.23 (s, 1H; CH), 8.06 (d, $^3J = 7.7$ Hz, 1H; CH), 7.15–7.25 (m, 2H; CH), 7.00 (t, $^3J = 8.4$ Hz, 1H; CH), 5.82 (s, 1H; CH), 5.40 (br s, 1H; NH), 3.88 (d, $^3J = 7.1$ Hz, 2H; CH_2), 3.30–3.12 (br m, 2H; CH_2), 2.38 (s, 3H; CH_3), 2.10–2.00 (m, 1H; CH), 2.00–1.92 (m, 1H; CH), 1.05–0.95 ppm (m, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 163.6$, 160.1, 155.5, 153.8, 137.8, 130.1, 128.2, 126.5, 123.3, 121.5, 86.8, 50.1, 49.2, 28.2, 26.7, 20.2, 20.1, 18.8 ppm; IR (KBr): $\tilde{\nu} = 3430$, 3034, 2964, 2872, 1687, 1599, 1550, 1460, 1152 cm^{-1}; MALDI-TOF: m/z calcd: 356.23; found: 356.25 $[M+H]^+$.

Capped N^4,N^6-diisobutylpyrimidine-4,6-diamine–tolyl urea-linked "trimer" (12): Compound **2** (0.11 g, 0.5 mmol) was placed in a flame-dried flask along with a stir bar. The flask was purged with nitrogen and

fitted with a nitrogen filled balloon, after which anhydrous toluene (2 mL) was added. *o*-Tolyl isocyanate (0.2 g, 1.5 mmol) was added dropwise and the solution was stirred at 90 °C for 48 h. The mixture was allowed to cool to room temperature and methanol (5 mL) was added to quench any remaining isocyanate. The solvent was evaporated and chloroform (10 mL) was added to the resulting white solid. The mixture was filtered to remove insoluble material, and the filtrate was purified by column chromatography (methylelene chloride/ethyl acetate, 9.5:0.5) to yield a cream-coloured solid in 75% yield (0.183 g). $R_f = 0.67$ (methylelene chloride/ethyl acetate, 9.5:0.5); m.p. = 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 12.55$ (s, 2H; NH), 8.58 (s, 1H; CH), 8.05 (d, $^3J = 8.2$ Hz, 2H; CH), 7.20–7.260 (m, 4H; CH), 7.06 (t, $^3J = 8.2$ Hz, 2H; CH), 6.43 (s, 1H; CH), 3.99 (br d, $^3J = 7.3$ Hz, 4H; CH_2), 2.42 (s, 6H; CH_3), 2.20–2.00 (m, 2H; CH), 1.05 ppm (d, $^3J = 6.7$ Hz, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 161.4$, 153.7, 153.4, 137.6, 130.6, 128.7, 127.0, 124.3, 122.2, 92.8, 50.8, 27.1, 20.4, 19.1 ppm; IR (KBr): $\tilde{\nu} = 3028$, 2965, 1694 1582, 1539, 1458, 1201, 1148 cm^{-1}; MALDI-TOF: *m*/*z* calcd: 489.29; found: 489.34 $[M+H]^+$

Uncapped N^4,N^6-diisobutylpyrimidine-4,6-diamine–tolyl urea-linked "trimer" (13): Compound **2** (1 g, 4.5 mmol) was placed in a flame-dried flask along with a stir bar. The flask was purged with nitrogen and fitted with a nitrogen filled balloon, after which anhydrous toluene (16 mL) was added. Tolylene-2,6-diisocyanate (0.3 mL, 2.1 mmol) was added dropwise and the solution was heated at 90 °C for 24 h. The solvent was evaporated to give a white solid, which was then re-dissolved in chloroform (10 mL). Insoluble material was removed by vacuum filtration. The filtrate was concentrated to half its volume and purified by column chromatography (chloroform/acetone, 8:2) to give a white solid in 44% yield (0.560 g). $R_f = 0.68$ (chloroform/acetone, 8:2); m.p. = 174–175 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 12.80$ (s, 2H; NH), 8.28 (s, 2H; CH), 7.65 (d, $^3J = 7.9$ Hz, 2H; CH), 7.20 (t, $^3J = 8.2$ Hz, 1H; CH), 5.80 (s, 2H; CH), 5.35 (br s, 1H; NH), 3.88 (br d, $^3J = 7.3$ Hz, 4H; CH_2), 3.20–3.12 (br m, 4H; CH_2), 2.35 (s, 3H; CH_3), 2.10–2.00 (m, 2H; CH), 2.00–1.92 (m, 2H; CH), 1.10–0.95 ppm (m, 24H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 163.5$, 160.2, 155.5, 154.1, 137.7, 126.2, 122.4, 119.5, 50.2, 49.2, 28.2, 26.7, 20.2, 20.1, 13.5 ppm; IR (KBr): $\tilde{\nu} = 3431$, 3027, 2964, 2973, 1686, 1596, 1551, 1470, 1216, 1153 cm^{-1}; MALDI-TOF: *m*/*z* calcd: 619.41; found: 619.64 $[M+H]^+$.

N^2,N^3-Diisobutylpyrazine-2,3-diamine uncapped urea-linked "trimer" (14): Compound **3** (0.50 g, 2.25 mmol) was placed in a flame-dried flask along with a stir bar. The flask was purged with nitrogen and fitted with a nitrogen filled balloon, after which anhydrous toluene (10 mL) was added. Tolylene-2,6-diisocyanate (0.16 mL, 1.12 mmol) was added dropwise and the solution was stirred at 90 °C for 24 h, after which additional tolylene-2,6-diisocyanate was added (0.050 mL, 0.35 mmol) and the solution was allowed to stir for an additional 24 h at 90 °C. The solvent was evaporated to give a brown gum, which was purified by column chromatography (chloroform/acetone, 8.5:1.5) to give a cream-coloured solid in 21% yield (0.130 g). $R_f = 0.49$ (chloroform/acetone, 8.5:1.5); m.p. = 198–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.04$ (d, $^3J = 2.4$ Hz, 2H; CH), 7.72 (d, $^3J = 2.4$ Hz, 2H; CH), 7.35 (d, $^3J = 7.8$ Hz, 2H; CH), 7.11 (t, $^3J = 7.8$ Hz, 1H; CH), 6.93 (s, 2H; NH), 4.99 (t, $^3J = 5.9$ Hz, 2H; NH), 3.55 (br s, 4H; CH_2), 3.29 (d, $^3J = 5.9$ Hz, 4H; CH_2), 2.01–1.85 (m, 7H; CH, CH_3), 0.96 (d, $^3J = 6.8$ Hz, 12H; CH_3), 0.91 ppm (d, $^3J = 6.8$ Hz, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 154.5$, 151.1, 141.9, 137.1, 136.8, 129.9, 126.4, 122.8, 119.9, 53.0, 48.6, 28.4, 28.2, 20.3, 20.2, 12.1 ppm; IR (KBr): $\tilde{\nu} = 3443$, 3020, 2962, 1682, 1505, 1472, 1213 cm^{-1}; MALDI-TOF: *m*/*z* calcd: 619.41; found: 619.50 $[M+H]^+$.

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