Cytosine modules in quadruple hydrogen bonded arrays

Elisabetta Greco,[a] Abil E. Aliev,[a] Valerie G. H. Lafitte,[a] Kason Bala,[b] David Duncan,[b] Laura Pilon,[b] Peter Golding[b] and Helen C. Hailes*[a]

Received (in Montpellier, France) 15th March 2010, Accepted 5th June 2010
DOI: 10.1039/c0nj00197j

Cytosine modules have been investigated for applications in supramolecular quadruple hydrogen bonded arrays. Notably, the importance of the C-5–H in the formation of unfolded and folded arrays by substitution to C-5–F was established. In addition, the incorporation of different alkyl chain lengths at N-1 and N-9 indicated that longer alkyl chains give rise to more of the unfolded rotamer, with the chain length and degree of unsaturation at N-1 having the major effect. Methyl cytosine modules were also able to readily form hetero-associated Upy–UCyt dimers as efficiently as the hexyl cytosine modules and a polyadipate telechelic polymer was used to prepare cytosine polymers.

Introduction

The design of supramolecular arrays based on non-covalent interactions, particularly hydrogen bonds, holds significant potential for the synthesis of new materials. For the range of properties required from supramolecular materials, there is a need for strong hydrogen bonded modules, which can be used in polymer or co-polymer synthesis *via* the self- or hetero-association of complementary units.[1–4] Self-complementary quadruple hydrogen bonding linear arrays comprised of two donors (DD) and two acceptors (AA), to give DDAA modules, have proven to be particularly effective.[3–5] These include the ureidopyrimidinones (UPy) **1**,[4] ureidonaphthyridine (UN) **2**[3b] and the recently described ureidocytosine (UCyt) modules **3**[5] reported by our group (Fig. 1). The DDAA modules reported have several features which can influence the resulting performance in arrays. For example, the UPy modules can exist in three different tautomeric forms depending on the environment and substituents attached, which can increase the complexity of the species present.[4] Despite this Upy DDAA arrays have been used in a range of polymeric materials, cyclic dimers have been reported, and redox materials incorporating ferrocene have been described.[4] Dimerization constants ($K_{\rm dim}$) when R′ is alkyl for the DDAA unit of approximately 10^7 M^{-1} in $CDCl_3$ were observed.[4c] Modules including **2** and **3** that do not undergo such tautomeric changes may be preferable for use in controlled material design. However, the replacement of NH moieties with CH groups results in removal of the intramolecular N–H···O hydrogen bond and some conformational flexibility in the ureido fragment between folded and unfolded forms.[3b,5] For example, the $K_{\rm dim}$ for UN dimer **2·2** (R is C_4H_9) in $CDCl_3$ was 1.1×10^2 M^{-1} but UCyt **3a** (R = R^1 = C_6H_{13}) formed the stable unfolded dimer **3a·3a** with a $K_{\rm dim} > 2.5 \times 10^5$ M^{-1} in $CDCl_3$ with some folded dimer present (5%). The unfolded dimer **3a·3a** also had a $K_{\rm dim} > 2 \times 10^7$ M^{-1} in C_6D_6.[3b,5]

[a] *Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ, UK. E-mail: h.c.hailes@ucl.ac.uk; Fax: +44 (0)20 7679 7463; Tel: +44 (0)20 7679 4654*
[b] *AWE plc., Aldermaston, Reading, Berkshire, RG7 4PR, UK*

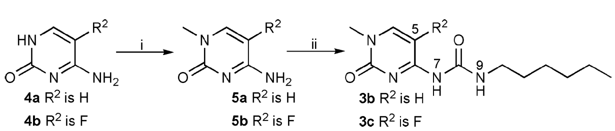
In addition, studies investigating heterodimeric arrays between **1** and **3** suggested that the UCyt DDAA unit competed well with the Upy module. One advantage of modules such as the ureidocytosines is that they can readily be functionalised at N-1, enabling the introduction of alternative moieties or properties into the arrays. In our current work we have investigated the effect of substituting the hydrogen at C-5 with fluorine, to determine the effect on the ratio of unfolded to folded conformers. Also alternative side groups at N-1 were introduced with a view to understanding the behaviour of the modules and identifying suitable modules for applications in polymer synthesis.

Results and discussion

In the ureido substituted cytosine, conformationally both folded (**3′**) and unfolded (**3**) forms may exist (Fig. 2), with the desired unfolded form stabilized by quadruple hydrogen bonding on dimerization. In previous work a single crystal XRD of **3a** (R = R^1 = C_6H_{13}) revealed that the side chain carbonyl (C-8=O) and the C-5–H of the ring were nearly planar with measured geometry in agreement with that for a weak hydrogen bond.[5]

Initial studies therefore investigated the role of C5-H in the formation of unfolded and folded arrays by substitution at R^2. Two analogues were prepared possessing a methyl group at R^1 and H or F at R^2 (Fig. 2 and Scheme 1).

There have been several reports in the literature for the conversion of cytosine (**4a**) into 1-methylcytosine (**5a**).[6,7] However, the most convenient method was found to be the use of a one-pot procedure and basic phase transfer conditions with aqueous tetrabutylammonium hydroxide which had been

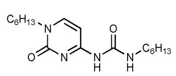
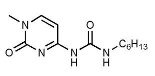
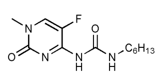


Scheme 1 Synthesis of **5a**, **5b**, **3b** and **3c**. *Reagents and conditions*: (i) 40% Bu_4NOH, CH_2Cl_2, MeI; **5a** 78%, **5b** 59%; (ii) $C_6H_{13}NCO$, pyr, 90 °C; **3b** 87%, **3c** 74%.

reported to generate **5a** in 45% yield.[8] Use of this procedure gave **5a** in 78% after purification by recrystallisation (Scheme 1). 5-Fluorocytosine (**4b**) was methylated at N-1 using the same procedure to give 5-fluoro-1-methylcytosine (**5b**) in 59% yield. Compounds **5a** and **5b** were then readily converted to the ureidocytosines **3b** and **3c**.

The ^{1}H NMR spectrum of **3b** in $CDCl_3$ at 298 K showed the two hydrogen bonded protons 7-H and 9-H at 10.9 and 9.0 ppm, respectively, confirming the involvement of 7-H and 9-H in a hydrogen bonding (Table 1). The chemical shifts were comparable to that of the previously described dihexyl analogue **3a** (Fig. 1; R = R^1 = C_6H_{13}) for 7-H and 9-H at 10.9 and 9.0 ppm when in the unfolded conformation and **3a·3a** DDAA dimeric array.[5] A 30 mM solution of **3b** in $CDCl_3$ was also studied by ^{1}H NMR at different temperatures because line broadening, due to an exchange process, was observed at 298 K for signals corresponding to 7-H and 9-H and 5-H. At 256 K the signals became much sharper together with the appearance of a second set of small signals at 9.7, 7.4 and 6.1 ppm, assignable to 9-H and 7-H (superimposed), 6-H and 5-H, respectively, of the folded rotamer **3b′**, in accordance with a previous detailed study on **3a**.[5] The change in chemical shift of 5-H from 7.5 ppm in unfolded **3b** to 6.1 ppm in folded **3b′** can be attributed to a loss of 5-H···O proximity and hydrogen bonding or magnetic anisotropy of the carbonyl group. Peak integration gave a ratio of 11 : 1 for **3b** : **3b′** with the unfolded rotamer **3b** the major species in $CDCl_3$. Overall these experiments indicated that **3b** in $CDCl_3$ formed a DDAA array **3b·3b** with the unfolded rotamer and that a small amount of the folded rotamer **3b′·3b′** was also present in a higher ratio (11 : 1) than that reported for **3a** (19 : 1) (Table 2).[5] In DMSO-d_6, a strong hydrogen bond acceptor, compound **3b** formed the folded rotamer as has been described for **3a**, and identical chemical shifts were observed (Table 1).

Table 1 Chemical shift for **3a–3c** for key ^{1}H NMR signals

Proton	**3a**[5] δ/ppm 	**3b** δ/ppm 	**3c** δ/ppm 
$CDCl_3$ at 298 K			
5-H	7.6	7.6	—
6-H	7.4	7.4	7.5
7-H	10.9	10.9	Not detected
9-H	9.0	9.0	9.1
$CDCl_3$ at 256 K			
5-H	7.5 (6.1 folded)	7.5 (6.1 folded)	—
6-H	7.5 (7.4 folded)	7.5 (7.4 folded)	7.5 (7.6 at 223 K)
7-H	11.1 (9.6 folded)	11.0 (9.7 folded)	7.7 (8.2 at 223 K)
9-H	9.0 (9.7 folded)	9.0 (9.7 folded)	9.2 (9.3 at 223 K)
DMSO-d_6			
5-H	6.2	6.2	—
6-H	7.9	7.9	8.3
7-H	9.7	9.7	9.8
9-H	9.0	9.0	9.4

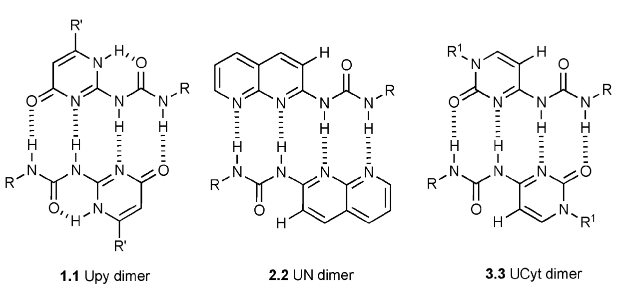


Fig. 1 DDAA module dimers **1·1**, **2·2**, and **3·3**.

^{1}H NMR spectroscopy data of the fluorinated analogue **3c** in solution indicated that in $CDCl_3$ only one rotamer was observed. At 298 K 7-H was not readily detected due to line broadening and possible superimposition with the chloroform signal. However at lower temperatures 7-H was clearly observed at 7–8 ppm, indicative of the folded rotamer **3c′** (Table 1), rather than at 11 ppm when in the DDAA array. Chemical shifts for 9-H were similar at both 298 K and 256 K, suggesting presence of the same folded rotamer. At low temperatures no further rotamers were detected, and in addition the temperature dependence of 7-H from 7.7 ppm to 8.2 ppm at 223 K, suggested population of a double hydrogen bonded dimer (**3c′·3c′**) on lowering the temperature.[5] Formation of the folded rotamer is consistent with destabilization of the unfolded rotamer by the removal of the H-bonding interaction between 5-H and O-8 of the cytosine unit. Upon formation of the folded rotamer an intramolecular H-bond between N-3 and 9-H (Fig. 2) will be formed.

Previously the single crystal XRD of **3a** revealed a short intermolecular distance between C-6–H and O=C-8 which seemed to order the dimeric system into infinite 1-D chains, suggesting that stacking-type interactions may be important in the interlayer separation of the dimers.[5] Also, the alkyl chains of the unit were not parallel to each other: while the hexyl chain attached to the urea bond was in the plane of the dimer, the hexyl group at N-1 deviated from the plane by approximately 70°. In addition to the π-stacking interactions and inter- and intramolecular hydrogen bonding the alkyl side chains at N-1 and N-9 may also influence dimer organisation, particularly at N-1 due to its deviation from the plane. A range of analogues were therefore prepared to investigate side chain variation in the formation of the unfolded array which is important when considering the construction of polymers conjugated at N-1 or N-9. Different alkyl chains were selected for attachment at N-1, where van der Waals interactions may influence array formation, and in addition alkene and alkyne groups for potential subsequent coupling *via* click or metathesis strategies. Two different alkyl chains were attached at N-9

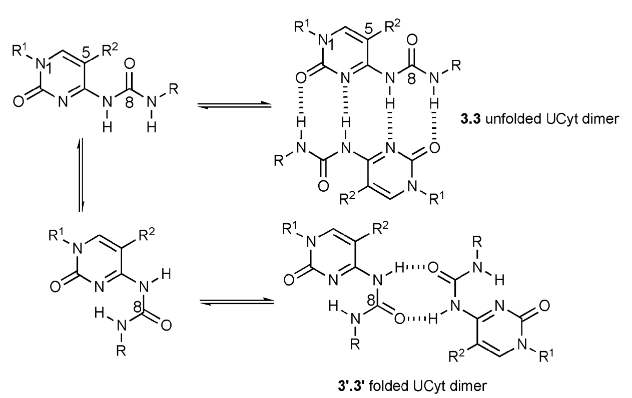


Fig. 2 Unfolded and folded form of dimers **3·3** and **3′·3′**.

Table 2 Compounds **3a–3m** and unfolded : folded ratio in $CDCl_3$

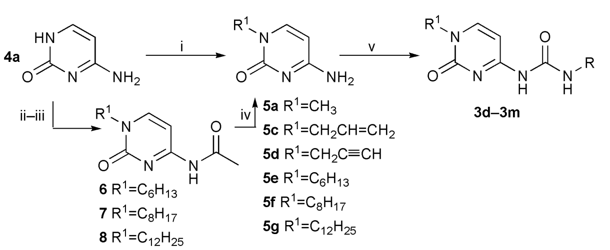
Compound	R^1 at N-1	R at N-9	Ratio[a] unfolded : folded
3a[5]	C_6H_{13}	C_6H_{13}	19 : 1
3b	CH_3	C_6H_{13}	11 : 1
3c	CH_3	C_6H_{13}	R^2 is F only folded
3d	CH_3	C_3H_7	9 : 1
3e	$CH_2CH{=}CH_2$	C_3H_7	3 : 1
3f	$CH_2CH{=}CH_2$	C_6H_{13}	13 : 1
3g	$CH_2C{\equiv}CH$	C_3H_7	7 : 1
3h	$CH_2C{\equiv}CH$	C_6H_{13}	8 : 1
3i	C_6H_{13}	C_3H_7	19 : 1
3j	C_8H_{17}	C_3H_7	15 : 1
3k	C_8H_{17}	C_6H_{13}	17 : 1
3l	$C_{12}H_{25}$	C_3H_7	17 : 1
3m	$C_{12}H_{25}$	C_6H_{13}	20 : 1

[a] Ratio measured at 256 K (**3a–3b**) and 248 K (**3d–3m**).

since they were in the plane of the dimer in **3a** and therefore expected to have less influence on the array formed.

The effect of R and R^1 on the ratio of unfolded to folded conformers was assessed in detail: when R^1 was C_6H_{13} and CH_3 (and R was C_6H_{13}) the ratios were 19 : 1 and 11 : 1 respectively. Cytosine analogues were prepared possessing allyl, propargyl, hexyl, octyl and dodecyl groups at R^1 and propyl and hexyl urea side chains at R. Compounds **3d–3m** were prepared as outlined in Scheme 2. The one-pot procedure and basic phase transfer conditions used to generate **5a** was also successfully used with allyl bromide and propargyl bromide to *N*-1 alkylate cytosine (**4a**) directly to **5c**[6] and **5d**,[9] in 45% and 81% yield respectively. This method was attempted with the longer chain alkyl bromides, but problems have been reported with competing *O*-2 as well as *N*-1 alkylation which was observed.[9] This is normally alleviated to some degree by using *N*-4-acetylcytosine. Accordingly, *N*-4-acetylcytosine was reacted under basic conditions with the corresponding alkyl bromide to give **6–8**.[5] Compounds **6–8** were then readily hydrolysed in ammoniacal methanol (7 N) to give **5e–5g**.[5,9] Urea formation was achieved using hexyl isocyanate and propyl isocyanate in pyridine and compounds **3d–3m** were formed in 16% to 92% yield (Scheme 2, Table 2), the yield being dependent on the scale of reaction and ease of purification.

Following the low temperature ^{1}H NMR method used for **3a** and **3b**, experiments were performed in order to assess the ratio of the major (unfolded) and minor (folded) rotamers and the data are summarised in Table 2. Analysis of **3a** and **3b** highlighted a decrease in the unfolded : folded ratio with a methyl group at N-1. For **3d**, also with a Me group at N-1, but propyl chain at N-9, a further small decrease in the ratio was observed. By comparison, for **3i**, with C_6H_{13} at N-1 and a propyl group at N-9, the ratio was 19 : 1, suggesting that the alkyl group at N-1 has the major influence on the conformer ratio, with the group at N-9 having a secondary (if any) effect. The other saturated longer chain analogues at R^1, **3j–3m**, possessed higher ratios of unfolded to folded conformers than **3b**, with the propyl groups at N-9 giving slightly lower ratios compared to hexyl moieties. This is consistent with enhanced van der Waals interactions for longer alkyl chains at N-1, stabilising intermolecular interactions and arrangement of the array into the unfolded conformer. With the alkyl group at N-9 in the plane of the dimer this is likely to have less influence on the dimeric array, as observed.



Scheme 2 Synthesis of **3a–3m**. *Reagents and conditions*: (i) 40% Bu_4NOH, CH_2Cl_2, R^1Br (R^1 = allyl, propargyl), 45% and 81%, respectively; (ii) Ac_2O, pyr or purchased; (iii) R^1Br, **7** 29%, **8** 71%; (iv) NH_3 in MeOH, **5f** 79%, **5g** 98%; (v) RNCO, 90 °C, **3d** 92%, **3e** 16%, **3f** 37%, **3g** 55%, **3h** 70%, **3i** 63%, **3j** 65%, **3k** 51%, **3l** 68%, **3m** 68%.

Interestingly, for the allyl analogues at N-1, **3e** and **3f** and particularly for **3e**, a low ratio of 3 : 1 was observed, possibly due to unfavourable destabilising side chain interactions, although **3f** with a hexyl chain at N-9 significantly increased this ratio. The propargyl side chain at N-1 gave rise to similar ratios for **3g** and **3h** (approximately 8 : 1), but again the value was lower than for saturated alkyl chains, possibly due to unfavourable π–π interactions and destabilisation of the linear AADD array. Overall, shorter alkyl and unsaturated chains at N-1 had the most marked effect, leading to lower unfolded : folded ratios, and the length of the side chain at N-9 had a secondary effect on the conformer ratio. This observation may be important when designing polymers linked *via* N-1 or N-9, or bifunctional polymers. To investigate this further, experiments with the methyl-cytosine unit were performed and polymers prepared.

The methyl-cytosine based modules were of interest because they gave moderate ratios (approximately 10 : 1) of unfolded : folded conformers, and were an ideal substrate to therefore probe whether the conformer ratio had a significant effect on the resulting conjugated polymers. They were also more synthetically accessible in high yield compared to the N-1 hexyl analogues. Initially, their use in heterodimeric arrays was explored further with the Upy analogues **1a** and **1b** possessing pendant propyl and hexyl alkyl groups, which were synthesised as previously described.[4f,10] This would establish their capacity to disrupt Upy dimerisation and assess whether the presence of the Me group at N-1 in **3**, and lower ratio of unfolded : folder conformation present in solution, would influence the array for applications in heterosupramolecular polymers. Interestingly, combinations of **1a** and **3d**, and **1b** and **3b** (Fig. 3) as a 1 : 1 mixture in $CDCl_3$ at 256 K revealed the ratio of **1·1** : **1·3** : **3·3** as approximately 5 : 6 : 5 which was identical to that previously reported for **1b** and **3a**.[5] This indicated that the methyl-cytosine based modules still competed well with Upy, despite the lower unfolded : folded ratio observed in $CDCl_3$ and that it would be suitable for applications in supramolecular polymers.

To provide a preliminary assessment of the methyl cytosine module compared to hexyl cytosine, and a Upy supramolecular material for comparison purposes, polymers were prepared. Accordingly, **5a**, **5e** and **9**[4g,11] were reacted with 1,6-dihexylisocyanate and the monoisocyanates formed were reacted with telechelic hydroxy terminated poly(2-methyl-1,3-propylene

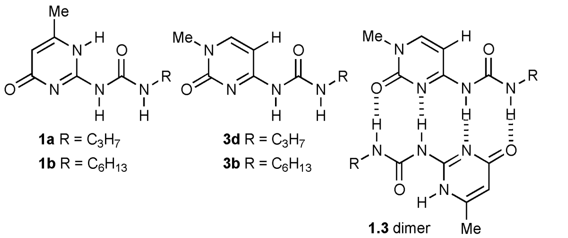


Fig. 3 Upy **1a**, **1b** and UCyt **3b**, **3d** used in hetero-association experiments and mixed heterodimer **1·3**.

adipate) (molecular weight 2000 g mol^{-1}) as a soft block, which has previously been used with difunctional Upys.[12] This gave polymers **10–12** (Scheme 3) and differential scanning calorimetry (DSC) of the polymers indicated similar glass transition temperatures of −45 °C for **10**, −49 °C for **11** and −44 °C for **12**.

These were comparable to a difunctional Upy polyadipate described with a T_g of −46 °C, and can also be compared to that of the propylene adipate prepolymer which has a T_g of −57 °C.[12] In addition, diffusion coefficient measurements of 20 mM solutions in $CDCl_3$ were performed to compare the degree of self-association of **11** and **12**. The measured values were 5.7×10^{-11} m^2 s^{-1} for **11** and 2.2×10^{-11} m^2 s^{-1} for **12** (compared to 2×10^{-10} m^2 s^{-1} for the telechelic polymer alone).[5] The diffusion rates were consistent with the presence of oligomers in solution in $CDCl_3$, and the faster diffusion rate for **11** suggested there existed slightly weaker hydrogen-bonding and polymerisation levels compared to **12**. Overall, the results from the heterodimeric arrays and polymer synthesis confirmed that methyl cytosine-based modules can readily be used in supramolecular synthesis, despite the lower ratio of unfolded to folded conformers observed in solution NMR studies.

Conclusions

In summary, the role of C-5–H in the cytosine module in the formation of unfolded and folded arrays by substitution at R^2 with F established that a weak hydrogen-bonding interaction is important to maintain the unfolded array. Substitution with a range of groups at N-1 indicated that longer alkyl chains give rise to more of the unfolded rotamer in solution NMR studies, but the presence of an allyl group lowers this significantly. In general, the chain length at N-9 only had a minor effect on the rotamer ratio, although this was dependent on the group at N-1 since for **3e** and **3f** the difference was more marked. *N*-Methyl cytosine modules were also able to disrupt Upy dimers and form hetero-associated Upy–UCyt dimers as efficiently as the *N*-hexyl cytosine modules, indicating its suitability for use in supramolecular polymer synthesis. Finally, a polyadipate telechelic polymer was used to prepare cytosine polymers which had similar properties to the analogous Upy-based polymer. These results will be used in future work when preparing bifunctional polymers and UCyt materials with polymers linked *via* N-1.

Experimental

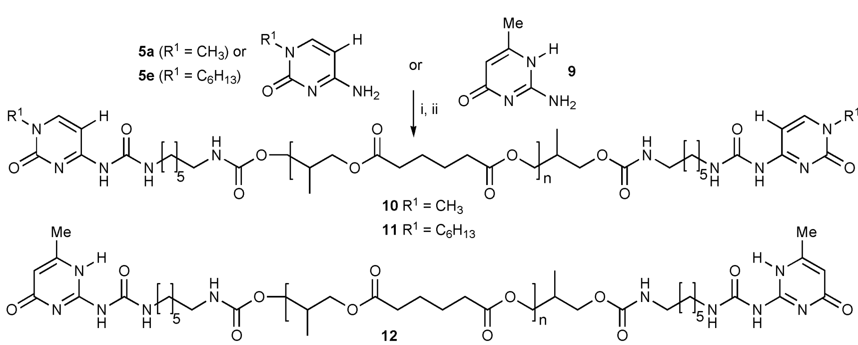
General methods

Unless otherwise noted, solvents and reagents were reagent grade from commercial suppliers and used without further purification. Anhydrous solvents were obtained using anhydrous alumina columns.[13] All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Reactions were monitored by TLC on Kieselgel 60 F_{254} plates with detection by UV, or permanganate, and phosphomolybdic acid stains. Flash column chromatography was carried out using silica gel (particle size 40–63 μm). Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at the field indicated. *J* values are given in Hz.

N-4-Acetylcytosine was prepared as previously described or purchased (Sigma-Aldrich).[14] Compounds **3a**, **5e**, and **6** were prepared as previously described.[5] The Upys **1a** and **1b** were synthesised using established procedures.[4f,10] 2-(6-Isocyanato-hexylaminocarbonylamino)-6-methyl-4[1*H*]pyrimidone was prepared as previously described.[11] Full details of methods for diffusion NMR experiments (all at 298 K) were previously described.[15]

Synthesis

1-Methyl-4-aminopyrimidin-2-(1*H*)-one (1-methylcytosine) 5a. To cytosine (1.66 g, 15.0 mmol) in CH_2Cl_2 (45 ml) was added tetrabutylammonium hydroxide (40% in water; 9.71 ml, 15.0 mmol). Methyl iodide (8.58 g, 60.0 mmol) was then added and the reaction stirred at rt for 18 h. Water was



Scheme 3 Synthesis of **10–12**. *Reagents and conditions*: (i) for **5a**, $OCN(CH_2)_6NCO$, CH_2Cl_2, 72 h at 40 °C; for **5e** and **9**, $OCN(CH_2)_6NCO$ CH_2Cl_2, 18 h at 40 °C; quantitative, 90%, 77%, respectively; (ii) hydroxy terminated polyadipate, dibutyltindilaurate, heat at reflux; 30%, 65%, 40% respectively.

added (150 ml), the mixture was extracted with CH_2Cl_2 (100 ml) and the aqueous layer was concentrated by rotary evaporation. The solid residue was recrystallized from ethanol to afford **5a** as a white solid (1.46 g, 78%). Mp 294–298 °C decomp. (EtOH) (lit. 296 °C, decomp.);[6] ^{1}H NMR (400 MHz; DMSO-d_6) δ 7.54 (1H, d, J 7.1 Hz, 6-H), 6.98 (2H, br s, NH_2), 5.59 (1H, d, J 7.1 Hz, 5-H), 3.18 (3H, s, NCH_3); m/z (ES+) 126 (MH$^+$, 100%).

5-Fluoro-1-methyl-4-aminopyrimidin-2-(1*H*)-one (5-fluoro-1-methylcytosine) 5b. To 5-fluorocytosine (1.00 g, 7.70 mmol), in 35 ml of CH_2Cl_2, was added 40% tetrabutylammonium hydroxide (40% in water; 5.00 ml, 7.72 mmol). The mixture was stirred at rt until the 5-fluorocytosine had dissolved. To the resulting solution, methyl iodide (4.43 g, 31.0 mmol) was added and the reaction was stirred at rt for 18 h. Water (100 ml) was added and the mixture extracted with CH_2Cl_2 (100 ml). The aqueous layer was concentrated *in vacuo* and the solid residue recrystallized from ethanol to afford **5b** as a white solid (0.65 g, 59%). Mp 275–280 °C (ethanol) (lit. 297–299 °C);[16] ν_{max}/cm^{-1} (solid) 3304, 3137, 3071, 1674, 1613; ^{1}H NMR (400 MHz; DMSO-d_6) δ 7.92 (1H, d, J_{HF} 6.0 Hz, 6-H), 7.48 (1H, br s, NH), 7.31 (1H, br s, NH), 3.16 (3H, s, NCH_3); ^{13}C NMR (75 MHz; DMSO-d_6) δ 157.3 (d, J_{CF} 12.7 Hz, C-4), 154.5 (C-2), 135.5 (d, J_{CF} 240 Hz, C-5) 131.2 (d, J_{CF} 30.7 Hz, C-6), 36.5 (CH$_3$N); ^{19}F NMR (282 MHz; DMSO-d_6) δ −170.5; ^{19}F CPD NMR (282 MHz; $CDCl_3$) δ −170.4 (d, $^3J_{HF}$ 6.0 Hz); m/z (ES+) 144 (MH$^+$, 60%); HRMS calculated for $C_5H_7FN_3O$ (MH$^+$) 144.05731, measured 144.05754.

1-(1-Methyl-2-oxo-1,2-dihydropyrimidin-4-yl)-3-hexyl urea 3b. To a solution of **5a** (200 mg, 1.60 mmol) in dry pyridine (10 ml) was added hexyl isocyanate (0.35 ml, 2.40 mmol). The resulting yellow solution was stirred at 90 °C for 16 h. The solution was cooled to rt, hexane was added and a white precipitate obtained which was collected by filtration, then washed with hexane to afford **3b** as a colourless solid (350 mg, 87%). Mp 206–208 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3214, 3044, 2958, 2926, 1696, 1642, 1621, 1599; ^{1}H NMR (400 MHz; $CDCl_3$) *major rotamer* δ 10.85 (1H, br s, NHCONHCH$_2$), 8.98 (1H, br s, NHCONHCH$_2$), 7.52 (1H, br s, 5-H), 7.45 (1H, d, J 7.3 Hz, 6-H), 3.47 (3H, s, CH_3N), 3.25 (2H, q, J 6.3 Hz, NHCH_2), 1.58 (2H, m, CH_2), 1.32 (6H, m, 3 × CH_2), 0.87 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz; $CDCl_3$) δ 165.1 (C-4), 157.7 (C-2), 154.3 (NHCONH), 147.2 (C-6), 97.4 (C-5), 40.1 (CH$_3$N), 38.0 (NCH$_2$), 31.5, 29.4, 26.6, 22.6, 14.0 (CH$_3$); m/z (ES+) 275 (MNa$^+$, 100%); HRMS calculated for $C_{12}H_{20}N_4NaO_2$ (MNa$^+$) 275.14839, measured 275.14789.

1-(5-Fluoro-1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)-3-hexyl-urea 3c. The reaction was carried out under anhydrous conditions. To a solution of **5b** (8.34 g, 66.6 mmol) in CH_2Cl_2 (250 ml) was added hexylisocyanate (64.7 ml, 400 mmol). The reaction was stirred at 40 °C for 72 h. Hexane was added and a white precipitate obtained. The product was collected by filtration to afford **3c** (15.1 g, 77%) as a white solid. Mp 160–164 °C (hexane); ν_{max}/cm^{-1} (solid) 3170, 2953, 1709, 1671, 1635; ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.14 (1H, br s), 7.46 (1H, d, J_{HF} 6.7 Hz, 6-H), 3.47 (3H, s, NCH_3), 3.33 (2H, q, J 6.8 Hz, NCH_2), 1.58 (2H, m, NCH$_2$CH_2), 1.31 (6H, m, 3 × CH_2), 0.89 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.3 (NHCOCH$_2$), 153.3 (d, J_{CF} 11.8 Hz, C-4), 152.3 (C-2), 134.8 (d, J_{CF} 242 Hz, C-5), 132.0 (d, J_{CF} 29.7 Hz, C-6), 40.4 (NCH$_3$), 38.4 (CH$_2$), 31.5 (CH$_2$), 29.6 (CH$_2$), 26.6 (CH$_2$), 22.6 (CH$_2$), 14.0 (CH$_3$); ^{19}F NMR (282 MHz; $CDCl_3$) δ −169.5; ^{19}F CPD NMR (282 MHz; $CDCl_3$) δ −169.5 (d, $^3J_{HF}$ 6.7 Hz); m/z (CI+) 271 (MH$^+$, 35%). 144 (100); HRMS calculated for $C_{12}H_{20}FN_4O_2$ (MH$^+$) 271.15702, measured 271.15725.

1-Allyl-4-aminopyrimidin-2-(1*H*)-one 5c. The reaction was carried out as described above for **5a** using cytosine (402 mg, 3.62 mmol), CH_2Cl_2 (15 ml), tetrabutylammonium hydroxide (40% in water; 2.34 ml, 3.62 mmol) and allyl bromide (1.20 ml, 14.0 mmol). The product was recrystallized from ethanol to afford **5c** as a white solid (240 mg, 44%). Mp 241–244 °C (EtOH) (lit. 242–245 °C);[17] ν_{max}/cm^{-1} (nujol) 3245, 2934, 1704, 1662; ^{1}H NMR (400 MHz; DMSO-d_6) δ 7.54 (1H, d, J 7.1 Hz, 6-H), 7.08 (2H, br, NH_2), 5.92 (1H, m, C=CHCH$_2$), 5.70 (1H, d, J 7.1 Hz, 5-H), 5.16 (1H, dd, J 10.3 and 1.5 Hz, HHC=CH), 5.10 (1H, J 17.1 and 1.5 Hz, HHC=CH), 4.29 (2H, m, NCH_2); ^{13}C NMR (150 MHz; $CDCl_3$) δ 163.0 (C-4), 155.1 (C-2), 144.1 (C-6), 130.4, 120.3, 96.7 (C-5), 50.8 (NCH$_2$); m/z (ES+) 152 (MH$^+$, 100%).

1-(Prop-2-ynyl)-4-aminopyrimidin-2-(1*H*)-one 5d. The reaction was carried out as described above for **5a** using cytosine (4.44 g, 40.0 mmol), CH_2Cl_2 (90 ml), tetrabutylammonium hydroxide (40% in water; 25.9 ml, 40.0 mmol) and propargyl bromide (12.7 ml, 160 mmol) and the reaction was stirred for 96 h. The product was recrystallized from ethanol to afford **5d** as a white solid (4.85 g, 81%).[9] ^{1}H NMR (400 MHz; DMSO-d_6) δ 7.63 (1H, d, J 7.2 Hz, 6-H), 7.20 (2H, br, NH$_2$), 5.72 (1H, d, J 7.2 Hz, 5-H), 4.46 (2H, m, CH_2N), 3.38 (1H, t, J 2.4 Hz HC≡C); m/z (ES+) 150 (MH$^+$, 100%).

***N*-(1-Octyl-2-oxo-1,2-dihydropyrimidin-4-yl)-acetamide 7.** To a solution of *N*-4-acetylcytosine (1.00 g, 6.53 mmol), in dry DMF (40 ml), was added anhydrous potassium carbonate (1.35 g, 9.80 mmol) and after 30 min 1-bromooctane (1.89 g, 9.80 mmol). The solution was heated at 80 °C for 24 h. Any residual solid was then removed by filtration and the filtrate evaporated under reduced pressure. The crude product was redissolved in $CHCl_3$ (100 ml) and washed with (1 N) HCl (100 ml), water (100 ml) and saturated sodium chloride solution (100 ml), then dried ($MgSO_4$). The solvents were evaporated *in vacuo* and the product purified using flash silica chromatography ($CHCl_3$/EtOAc 5 : 1 then $CHCl_3$/MeOH 9 : 1) to give **7** as a white solid (500 mg, 29%). Mp 122–124 °C ($CHCl_3$); ν_{max}/cm^{-1} (solid) 3229, 2922, 2851, 1693, 1670; ^{1}H NMR (600 MHz; $CDCl_3$) δ 10.51 (1H, s, NH), 7.60 (1H, d, J 7.2 Hz, 5-H), 7.41 (1H, d, J 7.2 Hz, 6-H), 3.85 (2H, t, J 7.2 Hz, CH_2N), 2.30 (3H, s, COCH_3), 1.73 (2H, m, CH_2), 1.20 (10H, m, 5 × CH_2), 0.86 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (150 MHz; $CDCl_3$) δ 171.5 (COCH$_3$), 163.0 (C-4), 155.7 (C-2), 148.7 (C-6), 96.8 (C-5), 51.1 (CH$_2$N), 31.7, 29.1, 28.9, 26.5 (signals superimposed), 24.8 (CH$_3$CO), 22.6, 14.2 (CH$_3$); m/z (ES+) 266 (MH$^+$, 100%), 225 (M − C_2OH^+, 15%);

HRMS calculated for $C_{14}H_{24}N_3O_2$ (MH^+) 266.18685, measured 266.18686.

***N*-(1-Dodecyl-2-oxo-1,2-dihydropyrimidin-4-yl)-acetamide 8.** To a solution of *N*-4-acetylcytosine (1.00 g, 6.53 mmol) in dry DMF (40 ml) was added anhydrous potassium carbonate (1.35 g, 9.80 mmol) followed after 30 min by 1-bromododecane (2.35 ml, 9.80 mmol). The solution was heated at 80 °C for 24 h. The residual solid was then removed by filtration and the filtrate evaporated under reduced pressure. The solid was redissolved in $CHCl_3$ and washed with HCl (1 N; 100 ml), water (100 ml) and saturated sodium chloride solution (100 ml), and the organic phase was dried ($MgSO_4$). The solvents were evaporated *in vacuo* and the crude solid purified using flash silica chromatography ($CHCl_3$/EtOAc 5 : 1 then $CHCl_3$/MeOH 9 : 1) to give **8** as a white solid (1.50 g, 71%). Mp 84–86 °C ($CHCl_3$); ν_{max}/cm^{-1} (solid) 3208, 2917, 2850, 1712, 1662; ^1H NMR (600 MHz; $CDCl_3$) δ 10.85 (1H, s, N*H*), 7.57 (1H, d, *J* 7.2 Hz, 5-H), 7.36 (1H, d, *J* 7.2 Hz, 6-H), 3.80 (2H, t, *J* 7.2 Hz, CH_2N), 2.20 (3H, s, COCH_3), 1.67 (2H, m, CH_2), 1.20 (18H, m, 9 × CH_2), 0.80 (3H, t, *J* 7.0 Hz, CH_3); ^{13}C NMR (150 MHz; $CDCl_3$) δ 171.7 ($COCH_3$), 163.1 (C-4), 155.8 (C-2), 148.7 (C-6), 96.9 (C-5), 50.9 (CH_2N), 31.9, 29.5, 29.2, 29.0, 28.8, 27.4, 26.8 (signals superimposed), 25.5 (CH_3CO), 22.7, 14.0 (CH_3); *m*/*z* (ES+) 322 (MH^+, 100%), 281 ($M - C_2OH^+$, 10); HRMS calculated for $C_{18}H_{32}N_3O_2$ (MH^+) 322.24945, measured 322.25039.

1-Octyl-4-aminopyrimidin-2-(1*H*)-one 5f. Compound **7** (480 mg, 1.81 mmol) was dissolved in ammonia in MeOH (7 N; 50 ml). The solution was stirred at rt in a sealed tube for 24 h. The solvent was evaporated *in vacuo* to afford a solid. Purification using flash silica chromatography ($CHCl_3$/MeOH 9 : 1 to 7 : 1) afforded **5f**[18] (320 mg, 79%). Mp 202–204 °C ($CHCl_3$); ν_{max}/cm^{-1} (solid) 3346, 3106, 2925, 2854, 1654; ^1H NMR (600 MHz; $CDCl_3$) δ 7.30 (1H, d, *J* 7.0 Hz, 6-H), 6.05 (1H, d, *J* 7.0 Hz, 5-H), 5.74 (2H, br s, NH_2), 3.74 (2H, t, *J* 7.1 Hz, CH_2N), 1.73 (2H, m, CH_2), 1.28 (10H, m, 5 × CH_2), 0.87 (3H, t, *J* 6.4 Hz, CH_3); ^{13}C NMR (150 MHz; $CDCl_3$) δ 164.6 (C-4), 156.0 (C-2), 145.8 (C-6), 94.9 (C-5), 50.2 (CH_2N), 31.7, 29.3, 29.2, 29.0, 26.5, 22.7, 14.1 (CH_3); *m*/*z* (ES+) 224 (MH^+, 100%); HRMS calculated for $C_{12}H_{22}N_3O$ (MH^+) 224.17629, measured 224.17675.

1-Dodecyl-4-aminopyrimidin-2-(1*H*)-one 5g. Compound **8** (450 mg, 1.42 mmol) was dissolved in ammonia in MeOH (7 N; 50 ml). The solution was stirred at rt in a sealed tube for 24 h. The solvent was evaporated *in vacuo* to afford a solid. Purification using flash silica chromatography ($CHCl_3$/MeOH 9 : 1 to 7 : 1) afforded **5g** as a colourless solid (390 mg, 98%). Mp 118–123 °C ($CHCl_3$); ν_{max}/cm^{-1} (solid) 3340, 3112, 2915, 2847, 1657; ^1H NMR (600 MHz; $CDCl_3$) δ 8.32 (1H, br s, N*H*), 7.30 (1H, d, *J* 7.3 Hz, 6-H), 6.15 (1H, d, *J* 7.3 Hz, 5-H), 5.81 (1H, br s, N*H*), 3.73 (2H, t, *J* 7.4 Hz, CH_2N), 1.67 (2H, m, CH_2), 1.27 (18H, m, 9 × CH_2), 0.87 (3H, t, *J* 7.0 Hz, CH_3); ^{13}C NMR (150 MHz; $CDCl_3$) δ 164.3 (C-4), 157.2 (C-2), 145.8 (C-6), 95.2 (C-5), 50.2 (CH_2N), 31.8, 29.6, 29.3, 29.1 (signals superimposed), 26.4, 22.6 (signals superimposed), 14.1 (CH_3); *m*/*z* (ES+) 280 (MH^+, 100%); HRMS calculated for $C_{16}H_{30}N_3O$ (MH^+) 280.23889, measured 280.23861.

1-(1-Methyl-2-oxo-1,2-dihydropyrimidin-4-yl)-3-propyl urea 3d. To a solution of **5a** (200 mg, 1.60 mmol) in dry pyridine (10 ml) was added propyl isocyanate (0.23 ml, 2.40 mmol). The reaction was stirred at 90 °C for 16 h, cooled to rt and hexane added. A white precipitate was formed which was collected by filtration and washed with hexane to afford **3d** as a colourless solid (310 mg, 92%). Mp 226–230 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3220, 3053, 2959, 1699, 1650, 1619, 1564; ^1H NMR (500 MHz; $CDCl_3$) *major rotamer* δ 10.83 (1H, br s, N*H*CONHCH$_2$), 8.97 (1H, br s, NHCON*H*CH$_2$), 7.57 (1H, br s, 5-H), 7.45 (1H, d, *J* 7.4 Hz, 6-H), 3.46 (3H, s, CH_3N), 3.19 (2H, q, *J* 6.0 Hz, NHCH_2), 1.57 (2H, m, CH_2), 0.96 (3H, t, *J* 7.4 Hz, CH_3); ^{13}C NMR (150 MHz; DMSO-d_6) δ 162.9 (C-4), 157.0 (C-2), 154.2 (NH*C*ONH), 149.7 (C-6), 93.6 (C-5), 39.3 (CH_3N), 37.1 (NCH_2), 23.0, 11.7 (CH_3); *m*/*z* (ES+) 211 (MH^+, 100%); HRMS calculated for $C_9H_{15}N_4O_2$ (MH^+) 210.11168, measured 210.11160.

1-(1-Allyl-2-oxo-1,2-dihydropyrimidin-4-yl)-3-propyl urea 3e. To a solution of **5c** (80 mg, 0.53 mmol) in dry pyridine (5 ml) was added propyl isocyanate (0.07 ml, 0.76 mmol). The reaction was stirred at 90 °C for 16 h, cooled to rt, hexane was added and the white precipitate formed collected by filtration then washed with hexane to afford **3e** as a colourless solid (20 mg, 16%). Mp 186–190 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3212, 3070, 2962, 1702, 1641, 1618; ^1H NMR (400 MHz; $CDCl_3$ at 248 K) δ 11.13 (1H, br s, N*H*CONHCH$_2$), 9.02 (1H, br s, NHCON*H*CH$_2$), 7.59 (1H, d, *J* 8.0 Hz, 5-H), 7.51 (1H, d, *J* 8.0 Hz, 6-H), 5.93 (1H, m, CH$_2$=C*H*), 5.32 (1H, d, *J* 12.0 Hz, C*H*H=CH), 5.22 (1H, d, *J* 16.0 Hz, CH*H*=CH), 4.50 (2H, d, *J* 4.0 Hz, NCH_2), 3.34 (2H, m, NHCONHCH_2), 1.56 (2H, m, CH_2), 0.90 (3H, m, CH_3); ^{13}C NMR (150 MHz; $CDCl_3$) δ 164.8 (C-4), 158.6 (C-2), 154.3 (NH*C*ONH), 146.3 (C-6), 131.8 (CH$_2$=*C*H), 119.5 (*C*H$_2$=CH), 97.7 (C-5), 59.2 (NCH_2), 42.0 (NCH_2), 22.9, 11.6 (CH_3); *m*/*z* (ES+) 237 (MH^+, 100%); HRMS calculated for $C_{11}H_{17}N_4O_2$ (MH^+) 237.12733, measured 237.13515.

1-(1-Allyl-2-oxo-1,2-dihydro-pyrimidin-4-yl)-3-hexyl urea 3f. To a solution of **5c** (150 mg, 0.99 mmol) in dry pyridine (10 ml) was added hexyl isocyanate (0.21 ml, 1.50 mmol). The reaction was stirred at 90 °C for 16 h. The solution was cooled to rt, hexane was added and a white precipitate obtained which was collected by filtration then washed with hexane to afford **3f** as a white solid (100 mg, 37%). Mp 198–200 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3212, 3054, 2928, 1699, 1654, 1614; ^1H NMR (400 MHz; $CDCl_3$) δ 10.91 (1H, br s, N*H*CONHCH$_2$), 8.99 (1H, br s, NHCON*H*CH$_2$), 7.61 (1H, br s, 5-H), 7.44 (1H, d, *J* 4.0 Hz, 6-H), 5.93 (1H, m, CH$_2$=C*H*), 5.32 (1H, d, *J* 8.0 Hz, C*H*H=CH), 5.26 (1H, d, *J* 16.0 Hz, CH*H*=CH), 4.47 (2H, m, NCH_2), 3.26 (2H, m, NHCH_2), 1.57 (2H, m, CH_2), 1.31 (6H, m, 3 × CH_2), 0.89 (3H, t, *J* 4.0 Hz, CH_3); ^{13}C NMR (150 MHz; $CDCl_3$) δ 165.0 (C-4), 157.1 (C-2), 154.2 (NH*C*ONH), 146.1 (C-6), 131.6 (CH$_2$=*C*H), 119.3 (*C*H$_2$=CH), 97.7 (C-5), 51.9 (NCH_2), 40.1 (NCH_2), 31.5, 29.4, 26.6, 22.6, 14.1 (CH_3); *m*/*z* (FAB+) 301 (MNa^+, 50%), 279 (MH^+, 100%), 242 (90); HRMS calculated for $C_{15}H_{24}N_4O_2$ (MH^+) 279.18209, measured 279.18212.

1-(2-Oxo-1-prop-2-ynyl-1,2-dihydropyrimidin-4-yl)-3-propyl urea 3g. To a solution of **5d** (150 mg, 1.00 mmol) in dry pyridine (9 ml) was added propyl isocyanate (0.14 ml, 1.50 mmol). The reaction was stirred at 90 °C for 16 h, then cooled down to rt, hexane was added and a white precipitate obtained which was collected by filtration and washed with hexane to afford **3g** as a white solid (130 mg, 55%). Mp 204–208 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3292, 3211, 3050, 2966, 2295, 1699, 1651, 1621, 1556; ^{1}H NMR (400 MHz; CDCl$_3$) δ 10.86 (1H, br s, N*H*CONHCH$_2$), 8.89 (1H, br s, NHCON*H*CH$_2$), 7.82 (1H, d, *J* 7.5 Hz, 6-H), 7.69 (1H, br s, 5-H), 4.67 (2H, m, NC*H*$_2$), 3.23 (2H, m, NHC*H*$_2$), 2.56 (1H, t, *J* 4.0 Hz, *H*CCCH$_2$), 1.61 (2H, m, C*H*$_2$), 0.91 (3H, t, *J* 7.2 Hz, C*H*$_3$); ^{13}C NMR (150 MHz; CDCl$_3$) δ 165.3 (C-4), 156.8 (C-2), 154.2 (NH*C*ONH), 144.9 (C-6), 98.1 (C-5), 76.6, 76.0, 42.0 (N*C*H$_2$), 38.8, 22.9, 11.7 (*C*H$_3$); *m*/*z* (EI) 234 (M$^+$, 10%), 205 (40), 176 (100); HRMS calculated for $C_{11}H_{14}N_4O_2$ (M$^+$) 234.11113, measured 234.11049.

1-(2-Oxo-1-prop-2-ynyl-1,2-dihydropyrimidin-4-yl)-3-hexyl urea 3h. To a solution of **5d** (1.00 g, 6.71 mmol) in dry pyridine (45 ml) was added hexyl isocyanate (1.46 ml, 10.0 mmol). The reaction was stirred at 90 °C for 16 h, then cooled to rt, hexane was added and a white precipitate obtained which was collected by filtration and washed with hexane to afford **3h** as a white solid (1.30 g, 70%). Mp 198–200 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3307, 3211, 3061, 2928, 2295, 1698, 1654, 1615, 1565; ^{1}H NMR (600 MHz; CDCl$_3$) δ 10.86 (1H, br s, N*H*CONHCH$_2$), 8.86 (1H, br s, NHCON*H*CH$_2$), 7.82 (1H, d, *J* 7.5 Hz, 6-H), 7.68 (1H, br s, 5-H), 4.67 (2H, m, NC*H*$_2$), 3.26 (2H, m, NHC*H*$_2$), 2.56 (1H, t, *J* 2.5 Hz, C*H*CCH$_2$), 1.52 (2H, m, C*H*$_2$), 1.36 (6H, m, 3 × C*H*$_2$), 0.88 (3H, t, *J* 5.5 Hz, C*H*$_3$); ^{13}C NMR (150 MHz; CDCl$_3$) δ 165.2 (C-4), 156.7 (C-2), 154.1 (NH*C*ONH), 144.8 (C-6), 98.0 (C-5), 76.4, 75.9, 40.2 (N*C*H$_2$), 38.7 (N*C*H$_2$), 31.6, 29.4, 26.7, 22.6, 14.1 (*C*H$_3$); *m*/*z* (FAB+) 299 (MNa$^+$, 70%), 277 (MH$^+$, 100); HRMS calculated for $C_{14}H_{21}N_4O_2$ (MH$^+$) 277.16644, measured 277.16681.

1-(1-Hexyl-2-oxo-1,2-dihydropyrimidin-4-yl)-3-propyl-urea 3i. To a solution of **5e** (100 mg, 0.51 mmol) in dry pyridine (10 ml) was added propyl isocyanate (0.07 ml, 0.77 mmol). The reaction was stirred at 90 °C for 16 h, cooled to rt, hexane was added and a white precipitate obtained which was collected by filtration and washed thoroughly with hexane to afford compound **3i** as a colourless solid (90 mg, 63%). Mp 218–220 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3308, 3211, 3056, 2925, 2853, 1698, 1651; ^{1}H NMR (600 MHz; CDCl$_3$) *major rotamer* δ 10.95 (1H, s, N*H*CONHCH$_2$), 9.00 (1H, br s, NHCON*H*CH$_2$), 7.55 (1H, br d, 5-H), 7.45 (1H, d, *J* 7.3 Hz, 6-H), 3.82 (2H, t, *J* 7.3 Hz, C*H*$_2$N), 3.22 (2H, m, NHCONHC*H*$_2$), 1.72 (2H, m, C*H*$_2$), 1.58 (2H, m, C*H*$_2$), 1.31 (6H, m, 3 × C*H*$_2$), 0.94 (3H, t, *J* 7.4 Hz, C*H*$_3$), 0.89 (3H, t, *J* 6.5 Hz, C*H*$_3$); ^{13}C NMR (150 MHz; CDCl$_3$) δ 165.0 (C-4), 157.4 (C-2), 154.5 (NH*C*ONH), 146.8 (C-6), 97.4 (C-5), 50.9 (*C*H$_2$N), 41.9 (N*C*H$_2$), 31.5, 29.0, 26.2, 22.8, 22.6, 14.1 (*C*H$_3$), 11.7 (*C*H$_3$); *m*/*z* (FAB+) 319 (MK$^+$, 100%), 281 (MH$^+$, 100%), 196 (50); HRMS (CI) calculated for $C_{14}H_{25}N_4O_2$ (MH$^+$) 281.19775, measured 281.19673.

1-(1-Octyl-2-oxo-1,2-dihydropyrimidin-4-yl)-3-propyl urea 3j. To a solution of **5f** (100 mg, 0.450 mmol) in dry pyridine (7 ml) was added propyl isocyanate (0.06 ml, 0.67 mmol). The reaction was stirred at 90 °C for 16 h, cooled to rt, hexane was added and a white precipitate obtained which was collected by filtration and washed thoroughly with hexane to afford compound **3j** as a colourless solid (90 mg, 65%). Mp 196–198 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3348, 3105, 2925, 2854, 1698, 1654; ^{1}H NMR (400 MHz; CDCl$_3$) *major rotamer* δ 10.96 (1H, s, N*H*CONHCH$_2$), 9.01 (1H, br s, NHCON*H*CH$_2$), 7.55 (1H, br, 5-H), 7.45 (1H, br d, *J* 8.0 Hz 6-H), 3.83 (2H, t, *J* 4.0 Hz, C*H*$_2$N), 3.22 (2H, m, NHCONHC*H*$_2$), 1.72 (2H, m, C*H*$_2$), 1.59 (2H, m, C*H*$_2$), 1.32 (10H, m, 5 × C*H*$_2$), 1.00 (3H, t, *J* 7.2 Hz, C*H*$_3$), 0.95 (3H, t, *J* 7.0 Hz, C*H*$_3$); ^{13}C NMR (150 MHz; CDCl$_3$) δ 164.8 (C-4), 157.2 (C-2), 154.4 (NH*C*ONH), 146.7 (C-6), 97.3 (C-5), 50.8 (*C*H$_2$N), 41.9 (N*C*H$_2$), 31.7, 29.1 (signals superimposed), 29.0, 26.5, 22.7, 22.6, 14.1 (*C*H$_3$), 11.5 (*C*H$_3$); *m*/*z* (ES+) 331 (MNa$^+$, 100%); HRMS (ES+) calculated for $C_{16}H_{28}N_4NaO_2$ (MNa$^+$) 331.2110, measured 331.2105.

1-(1-Octyl-2-oxo-1,2-dihydropyrimidin-4-yl)-3-hexyl urea 3k. To a solution of compound **5f** (100 mg, 0.450 mmol) in dry pyridine (7 ml) was added hexyl isocyanate (0.10 ml, 0.67 mmol). The reaction was stirred at 90 °C for 16 h, cooled to rt, hexane was added and a white precipitate obtained which was collected by filtration and washed thoroughly with hexane to afford compound **3k** as a white solid (80 mg, 51%). Mp 199–200 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3212, 3172, 3051, 2964, 2854, 1698, 1650; ^{1}H NMR (400 MHz; CDCl$_3$) δ 10.94 (1H, br s, N*H*CONHCH$_2$), 9.01 (1H, br s, NHCON*H*CH$_2$), 7.54 (1H, br), 7.45 (1H, br), 3.84 (2H, t, *J* 6.0 Hz, C*H*$_2$N), 3.25 (2H, m, NHCONHC*H*$_2$), 1.74 (2H, m, C*H*$_2$), 1.57 (2H, quint, *J* 7.0 Hz, C*H*$_2$), 1.30 (16H, m, 8 × C*H*$_2$), 0.90 (6H, t, *J* 4.0 Hz, 2 × C*H*$_3$); ^{13}C NMR (150 MHz; CDCl$_3$) δ 164.9 (C-4), 157.2 (C-2), 154.4 (NH*C*ONH), 146.7 (C-6), 97.3 (C-5), 50.8 (*C*H$_2$N), 40.2 (N*C*H$_2$), 31.6 (signals superimposed), 29.6, 29.4, 29.1 (signals superimposed), 26.7, 26.5, 22.6, 14.1 (*C*H$_3$); *m*/*z* (ES+) 373 (MNa$^+$, 100%); HRMS (ES+) calculated for $C_{19}H_{34}N_4NaO_2$ (MNa$^+$) 373.2579, measured 373.2588.

1-(1-Dodecyl-2-oxo-1,2-dihydropyrimidin-4-yl)-3-propyl urea 3l. To a solution of compound **5g** (150 mg, 0.540 mmol) in dry pyridine (10 ml) was added propyl isocyanate (0.07 ml, 0.80 mmol). The reaction was stirred at 90 °C for 16 h. The solution was then cooled down to room temperature, hexane was added and a white precipitate obtained which was collected by filtration and washed thoroughly with hexane to afford compound **3l** as a white solid (130 mg, 68%). Mp 198–200 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3213, 3173, 3053, 2962, 2918, 2851, 1699, 1650; ^{1}H NMR (600 MHz; CDCl$_3$) δ 10.95 (1H, s, N*H*CONHCH$_2$), 9.01 (1H, br s, NHCON*H*CH$_2$), 7.56 (1H, br s, 5-H), 7.43 (1H, d, *J* 5.5 Hz, 6-H), 3.82 (2H, t, *J* 7.2 Hz, C*H*$_2$N), 3.23 (2H, m, NHCONHC*H*$_2$), 1.73 (2H, m, C*H*$_2$), 1.60 (2H, m, C*H*$_2$), 1.28 (18H, m, 9 × C*H*$_2$), 0.96 (3H, t, *J* 7.3 Hz, C*H*$_3$), 0.89 (3H, t, *J* 7.0 Hz, C*H*$_3$); ^{13}C NMR (150 MHz; CDCl$_3$) δ 164.9 (C-4), 157.3 (C-2), 154.4 (NH*C*ONH), 146.7 (C-6), 97.3 (C-5), 50.8

(CH_2N), 41.8 (NCH_2), 31.9, 29.5 (signals superimposed), 29.0, 26.5, 22.7 (signals superimposed), 14.1 (CH_3), 11.6 (CH_3); *m*/*z* (CI+) 365 (MH^+, 100%); HRMS (CI+) calculated for $C_{20}H_{37}N_4O_2$ (MH^+) 365.29165, measured 365.29255.

1-(1-Dodecyl-2-oxo-1,2-dihydropyrimidin-4-yl)-3-hexyl urea 3m. To a solution of compound **5g** (150 mg, 0.540 mmol) in dry pyridine (10 ml) was added propyl isocyanate (0.07 ml, 0.80 mmol). The reaction was stirred at 90 °C for 16 h, cooled to rt, hexane was added and a white precipitate obtained which was collected by filtration and washed thoroughly with hexane to afford compound **3l** as a white solid (150 mg, 68%). Mp 188–190 °C (pyridine/hexane); ν_{max}/cm^{-1} (solid) 3308, 3211, 3059, 2925, 2849, 1699, 1651; ^{1}H NMR (400 MHz; $CDCl_3$) δ 10.94 (1H, br s, N*H*CONHCH$_2$), 9.00 (1H, br s, NHCON*H*CH$_2$), 7.56 (1H, br, 5-H), 7.45 (1H, br d, *J* 5.5 Hz 6-H), 3.82 (2H, t, *J* 7.1 Hz, C*H*$_2$N), 3.25 (2H, m, NHCONHC*H*$_2$), 1.72 (2H, m, C*H*$_2$), 1.57 (2H, quint, *J* 7.3 Hz, C*H*$_2$), 1.32 (24H, m, 12 × C*H*$_2$), 0.89 (6H, t, *J* 7.0 Hz, C*H*$_3$); ^{13}C NMR (150 MHz; $CDCl_3$) δ 164.9 (C-4), 157.3 (C-2), 154.4 (NH*C*ONH), 146.7 (C-6), 97.3 (C-5), 50.8 (*C*H$_2$N), 40.1 (N*C*H$_2$), 32.0, 31.9, 29.5 (signals superimposed), 29.2, 29.0, 26.7, 26.6, 26.5, 22.7, 22.6, 14.2 (*C*H$_3$), 14.1 (*C*H$_3$); *m*/*z* (CI+) 407 (MH^+, 75%), 280 (100); HRMS (CI+) calculated for $C_{23}H_{43}N_4O_2$ (MH^+) 407.33860, measured 407.33885.

1-(6-Isocyanatohexyl)-3-(1-methyl-2-oxo-1,2-dihydro-pyrimidin-4-yl)-urea. The reaction was carried out under anhydrous conditions. To a solution of **5a** (8.34 g, 66.6 mmol) in CH_2Cl_2 (250 ml) was added hexylisocyanate (64.7 ml, 400 mmol). The reaction was stirred at 40 °C for 72 h, hexane was added and the white precipitate was collected by filtration, giving the monourea which was directly used in the next step (19.6 g, quantitative). Mp 224–226 °C (hexane); ν_{max}/cm^{-1} (solid) 3312, 3047, 2930, 2858, 2260, 1698, 1657, 1620; ^{1}H NMR (400 MHz; $CDCl_3$) δ 10.84 (1H, br s, N*H*CONHCH$_2$), 9.06 (1H, br s, NHCON*H*CH$_2$), 7.58 (1H, br, 5-H), 7.44 (1H, d, *J* 7.3 Hz 6-H), 3.48 (3H, s, NC*H*$_3$), 3.28 (4H, m, NHCONHC*H*$_2$, C*H*$_2$NCO), 1.59 (4H, m, 2 × C*H*$_2$), 1.29 (4H, m, 2 × C*H*$_2$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 164.9 (C-4), 157.6 (C-2), 154.2 (NH*C*ONH), 147.3 (C-6), 121.7 (N*C*O), 97.2 (C-5), 42.7 (*C*H$_2$NCO), 40.8 (N*C*H$_3$), 39.8, 37.8, 31.0, 29.1, 26.1; *m*/*z* (ES+) 316 (MNa^+, 100%); HRMS (ES+) calculated for $C_{13}H_{19}N_5O_3Na$ (MNa^+) 316.13855, measured 316.13769.

1-(6-Isocyanatohexyl)-3-(1-hexyl-2-oxo-1,2-dihydro-pyrimidin-4-yl)-urea. The reaction was carried out under anhydrous conditions. To a solution of **5e** (1.50 g, 7.70 mmol) in dry CH_2Cl_2 (60 ml) was added hexylisocyanate (7.45 ml, 46.1 mmol). The reaction was stirred at rt for 15 h, hexane was added and the white precipitate was collected by filtration, giving the monourea which was directly used in the next step (2.50 g, 90%). Mp 191–193 °C (hexane); ν_{max}/cm^{-1} (solid) 3211–3293, 2964, 2286, 1700, 1653; ^{1}H NMR (400 MHz; $CDCl_3$) δ 10.90 (1H, br s, N*H*CONHCH$_2$), 9.06 (1H, br s, NHCON*H*CH$_2$), 7.54 (1H, br, 5-H), 7.43 (1H, d, *J* 7.2 Hz 6-H), 3.81 (2H, t, *J* 7.2 Hz, NC*H*$_2$), 3.27 (4H, m, NHCONHC*H*$_2$, C*H*$_2$NCO), 1.71 (2H, m, C*H*$_2$), 1.65 (4H, m, 2 × C*H*$_2$), 1.40 (4H, m, 2 × C*H*$_2$), 1.29 (6H, m, 3 × C*H*$_2$), 0.88 (3H, t, *J* 5.2 Hz, C*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 164.6 (C-4), 155.1 (C-2), 154.3 (NH*C*ONH), 146.6 (C-6), 121.8 (N*C*O), 97.3 (C-5), 50.7 (*C*H$_2$N), 42.8 (*C*H$_2$NCO), 39.8, 31.1, 28.8, 28.0, 27.9, 27.4, 23.0, 22.4, 22.0, 13.9 (*C*H$_3$); *m*/*z* (ES+) 386 (MNa^+, 30%), 364 (MH^+, 100); HRMS (ES+) calculated for $C_{18}H_{30}N_5O_3Na$ (MH^+) 364.23570, measured 364.23490.

Synthesis of polymers 10–12. The procedure for **10** is given below. To a solution of hydroxy terminated poly(2-methyl-1,3-propylene adipate) (MW 2000 g mol^{-1}) (0.682 g, 0.34 mmol), in chloroform (15 ml), was added 1-(6-isocyanato-hexyl)-3-(1-methyl-2-oxo-1,2-dihydro-pyrimidin-4-yl)-urea (0.300 mg, 1.02 mmol) and one drop of dibutyltindilaurate. The reaction mixture was heated at reflux for 20 h, chloroform (10 ml) was then added and the mixture was filtered to remove the excess of monoisocyanate. The filtrate was concentrated down to 10 ml, and silica gel (200 mg) was added with a further drop of dibutyltindilaurate and the solution was heated at 60 °C for 2 h. The silica gel was then removed by filtration and the chloroform was evaporated *in vacuo* to give the polymers which were purified using flash silica chromatography ($CHCl_3$/MeOH, 20 : 1 to 10 : 1) where required.

Polymer **10** was generated in 30% yield, as an opaque flexible plastic. ^{1}H NMR (400 MHz; $CDCl_3$) δ 10.81 (2H, br s, 7-H), 9.01 (2H, br s, 9-H), 7.52 (2H, br s, 5-H), 7.45 (2H, d, *J* 7.1 Hz, 6-H), 4.82 (2H, br s, N*H*COO), 3.96 (40H, m, C*H*$_2$OOC, C*H*$_2$OCONH), 3.47 (6H, s, C*H*$_3$N), 3.26 (4H, br q, NHCONHC*H*$_2$), 3.12 (4H, br q, *J* 6.3 Hz, C*H*$_2$NHCOO), 2.32 (36H, m, C*H*$_2$COO), 2.11 (10H, m, C*H*CH$_3$), 1.64 (52H, m, NHCH$_2$C*H*$_2$, OCH$_2$C*H*$_2$, C*H*$_2$), 0.95 (30H, d, *J* 6.9 Hz, C*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 173.1 (CH$_2$*C*OO), 160.4 (C-4), 157.8 (NH*C*OO), 156.4 (C-2), 154.2 (NH*C*ONH), 147.3 (C-6), 65.6, 40.8, 39.7, 38.0, 33.6, 32.6, 29.7, 29.3, 26.3, 24.2, 13.7.

Polymer **11** was generated using the same method as for **10** in 65% yield, as an opaque brittle solid. ^{1}H NMR (400 MHz; $CDCl_3$) δ 10.89 (2H, br s, 7-H), 8.98 (2H, br s, 9-H), 7.50 (2H, br s, 5-H), 7.42 (2H, d, *J* 7.2 Hz, 6-H), 4.80 (2H, br s, N*H*COO), 3.95 (38H, m, C*H*$_2$OOC, C*H*$_2$OCONH), 3.81 (4H, t, *J* 7.2 Hz, C*H*$_2$N), 3.20 (4H, br q, NHCONHC*H*$_2$), 3.10 (4H, br q, C*H*$_2$NHCOO), 2.32 (36H, m, C*H*$_2$COO), 2.07 (10H, m, C*H*CH$_3$), 1.64–1.27 (68H, m, NHCH$_2$C*H*$_2$, OCH$_2$C*H*$_2$, C*H*$_2$), 0.95 (30H, t, *J* 6.9 Hz, C*H*$_3$), 0.84 (6H, m, 2 × CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz; $CDCl_3$) δ 173.1 (CH$_2$*C*OO), 164.7 (C-4), 157.1 (NH*C*OO), 156.4 (C-2), 154.3 (NH*C*ONH), 146.7 (C-6), 97.2 (C-5), 65.8 (*C*H$_2$OCONH), 65.6 (*C*H$_2$OOC), 50.6 (*C*H$_2$N), 40.7, 39.7, 33.6, 31.2, 29.5 (signals superimposed), 26.4, 24.2, 22.5, 13.8, 13.7.

Polymer **12** was generated using the same method as for **10** in 40% yield, as an opaque flexible plastic. ^{1}H NMR (400 MHz; $CDCl_3$) δ 13.07 (2H, s, 1-H), 11.80 (2H, s, 7-H), 10.08 (2H, s, 9-H), 5.78 (2H, s, 5-H), 4.90 (2H, s, N*H*COO), 3.94 (40H, m, 20 × OC*H*$_2$), 3.21 (4H, m, NHCONHC*H*$_2$), 3.12 (4H, m, C*H*$_2$NHCOO), 2.28 (40H, m, C*H*$_2$OCO, C*H*$_2$COO, C*H*$_2$OCONH), 2.21 (6H, s, 2 × C*H*$_3$), 2.12 (10H, oct, *J* 6.3 Hz, C*H*CH$_3$), 1.64 (44H, m, 22 × C*H*$_2$), 0.95 (33H, d, *J* 6.9 Hz, C*H*$_3$CH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 173.1 (C-4), 156.5 (NH*C*OO), 156.4 (NH*C*ONH), 154.6 (C-2), 148.2 (C-6), 106.5 (C-5), 65.7 (O*C*H$_2$), 40.6, 39.5, 33.7, 31.8, 29.6, 29.4, 26.6, 26.2, 24.2, 13.8.

Acknowledgements

We thank AWE plc. for studentships (V.G.H.L. and E.G.).

Notes and references

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