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A convenient, high-yield synthesis of 1-substituted uracil and thymine derivatives

Dominik Rejman *, Soňa Kovačková, Radek Pohl, Martin Dračínský, Pavel Fiedler, Ivan Rosenberg *

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic

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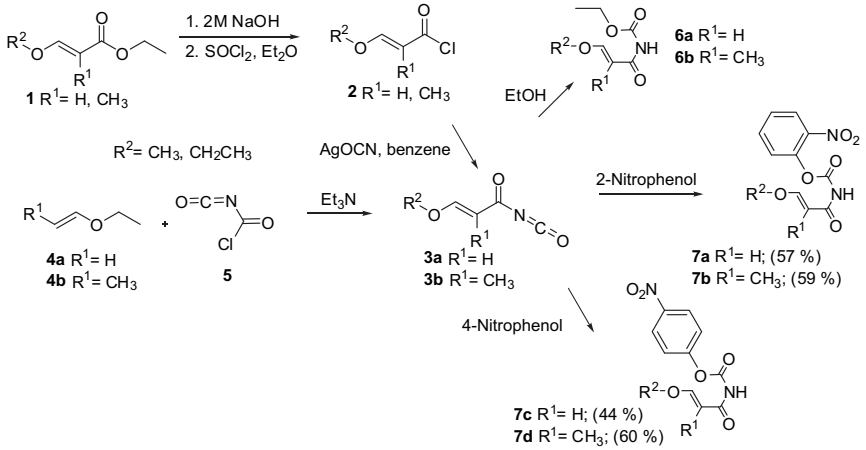
ABSTRACT

Novel reagents for the synthesis of 1-substituted uracil and thymine derivatives have been developed. The aminolysis of 2- or 4-nitrophenyl 3-ethoxyacryloylcarbamate and 3-ethoxy-2-methylacryloylcarbamate with a variety of primary amino derivatives proceeded smoothly under very mild reaction conditions yielding almost quantitatively the 1,3-disubstituted urea derivatives. Their subsequent cyclization provided the 1-substituted uracil and thymine compounds, in almost quantitative yield.

1. Introduction

Nucleosidation is often a crucial step in the synthesis of analogues of nucleosides. Purine nucleoside analogues are usually prepared via direct alkylation of the appropriate nucleobases (adenine, 2-amino-6-chloropurine, etc.) with the halo, tosyloxy, or mesyloxy derivatives,[1–4] or under Mitsunobu conditions.[2,3] However, all of these methods for the introduction of pyrimidine nucleobases (uracil, thymine, and cytosine) suffer from both low regioselectivity and yield of the 1-*N*-substituted product.[2,3] In some cases, the direct alkylation of nucleobases is accompanied by a competing elimination reaction which further decreases the yield of the desired compounds. As an alternative approach to the pyrimidine nucleoside analogues (e.g., carbocyclic nucleosides), a synthesis of 1-*N*-substituted nucleobases starting from a primary amine and isocyanate **3** or carbamate **6** was described fifty years ago by Shaw and Warrener.[5] The key isocyanates **3**, accessible by two independent routes[6,7] (Scheme 1), were used as intermediates for the synthesis of carbamates **6** described by Hřebabecký.[8]



Scheme 1.

Isocyanates **3** are extremely moisture-sensitive species and also very reactive compounds capable of forming carbamates with free hydroxy groups.[9] The reaction, therefore, is usually carried out either with the appropriately protected substrate or without protection at low temperature.

The formation of uracil and thymine rings is a two-stage reaction consisting of the aminolysis of carbamate **6** or the addition of amine to isocyanate **3** followed by a cyclization of the formed acryloylurea **9**

* Corresponding authors. Tel.: +420 220 183 381.
E-mail addresses: rejman@uochb.cas.cz (D. Rejman), ivan@uochb.cas.cz (I. Rosenberg).

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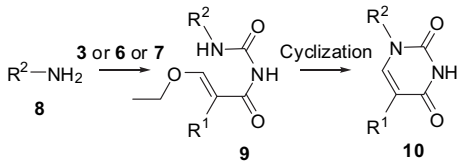
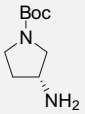
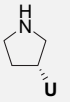
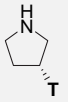
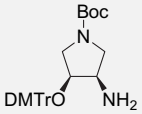
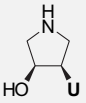
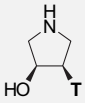
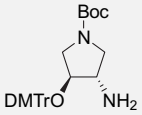
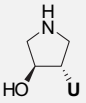
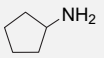
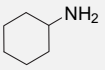
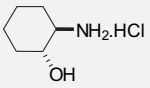
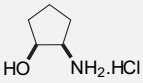
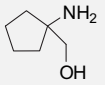
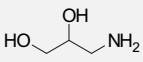
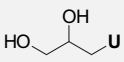
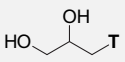
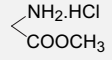
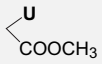
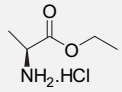
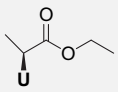
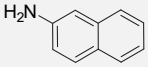
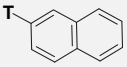
(Scheme 2). Both basic (aqueous alkali or ammonia, tertiary amines in organic solvent) and acidic (organic or inorganic acids in either aqueous or organic solvents) conditions were described for the cyclization of the ureas. Best results were obtained with aqueous sulfuric acid or 15 M aqueous ammonia according to Shealy and Dell.[10]



Scheme 2.

Recently we described the synthesis of pyrrolidine nucleoside analogues using alkylation of purine and pyrimidine nucleobases with various pyrrolidine mesyloxy derivatives.[2–4] In contrast to the purine nucleobases, the yields and regioselectivity of alkylations of pyrimidine nucleobases are unsatisfactory. Therefore, we attempted to use Hřebabecký's[8] reagents **6a** and **6b** for the synthesis of uracil and thymine rings to obtain pyrrolidine compounds **10b** and **10n** (Table 1), respectively. While the 'thymine reagent' **6b** provided a moderate yield of **10n**, the 'uracil reagent' **6a** yielded no product **10b** at all. In the latter case, we only

Table 1
Synthesis of uracil and thymine derivatives using reagents **7a** and **7b**

RNH_2 **8**		**9**/Yield% R^1=H	**10**/Yield%	Overall yield **U**%	**9**/Yield% R^1=CH_3	**10**/Yield%	Overall yield **T**%
a		**a**/85	**a**/97 	82(30)[3]	**m**/96	**m**/93 	89(29)[3]
b		**b**/87	**b**/90 	78	**n**/99	**n**/90 	89(24)[4]
c		**c**/90	**c**/80 	72	—	—	—
d		**d**/88	**d**/98 	86 (11)[23]	—	—	—
e		**e**/88	**e**/99 	87	**o**/82	**o**/95 	**77**
f		**f**/99	**f**/78 	77 (40)[24]	**p** /78	**p**/96 	75(18)[24]
g		**g**/95	**g**/95 	90 (15)[25]	—	—	—
h		**h**/88	**h**/92 	81	**q**/89	**q**/97 	86
i		**i**/87	**i**/98 	85(69)[26]	**r** /63(76)[a]	**r**/97 	61(45)[27]
j		**j**/94	**j**/96 	90 (63)[28]	**s**/87	**s**/99 	86 (59)[28]
k		**k**/87	**k**/84 	73 (76)[29]	—	—	—
l		**l**/87	**l**/96 	83	—	—	—
m		—	—	—	**t**/90	**t**/97 	87

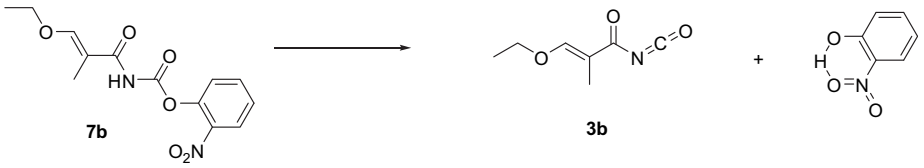
Urea derivatives **9a–l** and **9m–t** were synthesized using **7a** and **7b**, respectively. All cyclizations od **9–10** were carried out with Dowex 50 in H^+ form.
[a] When **7d** was used, we obtained **9r** in 76% yield instead of a 64% one obtained with **7b**.

observed the reagent decomposition. We concluded that we needed a reagent more reactive than **6a** and **6b** that would be able to react with the primary amine under milder conditions but which, at the same time, would not be as reactive as the isocyanates **3a**–**b**. We wanted to avoid the use of these moisture-sensitive and extremely reactive agents, which can react with the unprotected hydroxy groups. This property seems to be a main factor responsible for the varying yield of the reported uracil and thymine derivatives (usually ~20–80%, in most cases <60%) found in the literature.[11–22] We decided, therefore, to modify the original Hřebabecký's reagents **6**[8] by exchanging the ethyl ester group for a more reactive nitrophenyl one.

2. Results and discussions

The synthesis of the reagents **7a** and **7b** followed the procedure described for **6**,[8] whereby in the last step of this 'one pot' synthesis, a 2-nitrophenol solution in dioxane was added instead of ethanol. The reaction mixture was then concentrated in vacuo and the desired product was obtained by a crystallization from a mixture of toluene and petroleum ether. All procedures were carried out under strict exclusion of moisture under an argon atmosphere. By the same synthetic route we also prepared the 4-nitrophenyl esters **7c** but in a lower yield than **7a** (44% and 57%, resp.) due to a more difficult crystallization of **7c**.

The 'uracil reagents' **7a** and **7c** were fully characterized by NMR, MS, and elemental analysis. On the other hand, the characterization of the 'thymine reagent' **7b** appeared to be more difficult due to its unexpectedly high reactivity. The ^{1}H NMR spectrum of **7b** recorded in commercial grade $CDCl_3$ showed a mixture of at least four compounds identified as 3-ethoxy-2-methylacryloylcarbamic acid, 3-ethoxy-2-methylacryloylamide (as the product of decarboxylation of the former compound), 2-nitrophenol, and **7b**. If the measurement was performed in $CDCl_3$ adjusted prior to use by passing it through a short pad of anhydrous potassium carbonate, the spectrum did show the appropriate, expected signals of the reagent **7b** but still in the course of the data acquisition (~1 h), the signals of **7b** gradually disappeared and the signals of 2-nitrophenol and isocyanate **3b** appeared instead. When dry methanol was added to the solution of **7b** in NMR cuvette (in any stage of the NMR measurement), the immediate formation of the methyl ester **11** (~90%) was observed. The IR spectrum recorded in potassium carbonate-treated $CDCl_3$ showed the presence of the isocyanate moiety (band at 2244, w). These results clearly showed that the high reactivity of **7b** is caused, in fact, by the presence of isocyanate **3b** formed by the spontaneous elimination of 2-nitrophenol from **7b** (Scheme 3). In contrast to **7b**, the 4-nitrophenyl ester **7d** was found to be stable in untreated (commercial grade) $CDCl_3$ so that NMR spectra could be easily recorded.



Scheme 3.

The mechanism of the instability of **7b** in the solution is unclear. A detailed study on the reaction kinetics, along with the ab initio calculations, which would explain this phenomenon and especially the differences in reactivity of nitrophenyl esters **7a**–**7d**, is underway.

The prepared reagents **7a** and **7b** were used for the synthesis of desired pyrrolidine nucleosides **10a**–**c** and **10m**,**n** in very good yields (see Table 1). A more detailed study on these pyrrolidine nucleosides, as well as the conformational study, will be published elsewhere. The properties of reagents **7a** and **7b** were further evaluated with a series of commercially available amines **8d**–**m**. The reactivity of the 4-nitrophenyl 'uracil reagent' **7c** was identical with that of 2-nitrophenyl ester **7a** (data not shown). The reactions were carried out according to the Scheme 2. The results are summarized in Table 1 (yields given in parentheses refer to the cited literature). In all cases, the cyclization was accomplished by heating the respective urea derivatives **9a**–**t** with Dowex 50 (H^+ form) in dioxane. Excellent yields of uracil and thymine derivatives were obtained in all cases, as obvious from Table 1.

In the case of free amines, the aminolysis proceeded in dioxane at room temperature. In the case of amine hydrochlorides, the reaction was carried out in DMF with 1 equiv of DBU to release the free amine for the aminolysis. Because of high reactivity of 'thymine reagent' **7b** toward amines bearing free hydroxy groups, the reaction was performed in DMF at −20 °C to suppress potentially competing reaction with hydroxyls and thus obtain optimal results. When performing the reaction at room temperature, the formation of side products was observed. A lower yield (63%) of the urea derivative **9r** originating from 3-aminopropane-1,2-diol (**8i**) seems to be very probably caused by the presence of moisture in the amine **8i**. We repeated the synthesis of **10r** with the reagent **7d**. The aminolysis was carried out in dioxane at rt whereby the urea derivative **9r** was obtained in 76% yield.

Simple amines **8d**,**e**, as well as the aromatic amines **8j** and **8m**, afforded excellent yields in both aminolysis and cyclization reaction. To show the usefulness of the reagents in the case of amines containing free hydroxy groups, the compounds **8f**–**i** were selected as a starting material. Amino acid esters **8k**,**l** were also evaluated, in order to widen the scope of the novel reagent's utility.

3. Conclusion

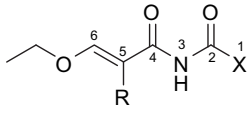
In conclusion, the synthesis of novel, versatile reagents for uracil (**7a**,**7c**) and thymine (**7b**,**7d**) introduction giving consistently high yields has been developed and its practical usefulness proved. The smooth formation of 1,3-disubstituted urea derivatives and, thus, a broad versatility of the prepared carbamates was proved using a variety of structurally diverse amines containing also free hydroxyl functionalities. The reagents are crystalline solids and can be stored for a long time at rt (**7a**,**7c**, and **7d**) or in freezer (**7b**). The use of the 4-nitrophenyl derivatives **7c** and **7d** is highly recommended for the introduction of uracil and thymine moieties, respectively, because of their optimal reactivity and high stability. The use of the 4-nitrophenyl esters of 2-substituted 3-ethoxyacryloylcarbamates is beneficial for the synthesis of 5-substituted uracil derivatives, because high yields are achieved while the method is preparatively simple.

4. Experimental

4.1. General

Unless stated otherwise, all used solvents were anhydrous. Amines **8d**–**m** were purchased from Sigma-Aldrich (Czech Republic) and used directly. TLC was performed on UV 254 silica gel

pre-coated aluminum plates (Merck). Compounds were detected by UV light (254 nm) and/or by spraying with 1% ethanolic solution of ninhydrin to visualize amines. Preparative column chromatography was carried out on silica gel (40–60 μm; Fluka), and the elution was performed at the flow rate of 40 ml/min. The following solvent systems were used for TLC and the preparative chromatography: toluene/ethyl acetate 1:1 (T); chloroform/ethanol 9:1 (C1). The concentrations of solvent systems are stated in volume percents. Analytical RP HPLC was performed on LC5000 Liquid Chromatograph (INGOS-PIKRON, Czech Republic) using Luna C18 (2) column (4.6×150 mm) at a flow rate of 1 ml/min under gradient elution of methanol in 0.1 M TEAA pH 7.5 (*A*=0.1 M TEAA; *B*=0.1 M TEAA in 50% aqueous methanol; C=methanol). Mass spectra were recorded on LTQ Orbitrap XL (Thermo Fisher Scientific) instrument using ESI method. Bruker AVANCE 500 (^{1}H at 500 MHz, ^{13}C at 125.7 MHz) and Bruker AVANCE 600 (^{1}H at 600.1 MHz, ^{13}C at 150.9 MHz) spectrometers were used for NMR spectra measurement. Chemical shifts (in ppm, δ scale) were referenced to TMS as internal standard or to a solvent signal; coupling constants (*J*) are given in Hz. Complete assignment of protons and carbons was done by analysis of correlated homonuclear 2D-COSY and heteronuclear ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra. Relative configuration was checked using DPFGSE-NOE and 2D-ROESY techniques. Nucleobase atom numbering was used also in the case of linear intermediates:



4.2. General method for aminolysis A

Reagent **7a**, **7c** or **7d** (1.1 equiv) or **7b** (1.3 equiv) was added to the solution of amine in dioxane (10 ml/mmol), and the reaction mixture was stirred at rt for 20 min. Solvent was removed in vacuo and the product was obtained by column chromatography on silica gel using a linear gradient of ethyl acetate in toluene.

4.3. General method for aminolysis B

Reagent **7b** (1.3 equiv) was added to the solution of amine in DMF (10 ml/mmol) at −20 °C. The reaction mixture was stirred at −20 °C for 20 min. Solvent was removed in vacuo and the product was recovered using column chromatography on silica gel under a linear gradient of ethyl acetate in toluene.

4.4. General method for aminolysis C

Reagent **7a** (1.1 equiv) or **7b** (1.3 equiv) was added to the solution of amine and DBU (1 equiv) in DMF (10 ml/mmol). The reaction mixture was stirred at rt for 20 min. Solvent was removed in vacuo and the product was obtained by column chromatography on silica gel using a linear gradient of ethyl acetate in toluene.

4.5. General method for aminolysis D

Reagent **7b** (1.3 equiv) was added to the solution of amine and DBU (1 equiv) in DMF (10 ml/mmol) at −20 °C. The reaction mixture was stirred at −20 °C for 20 min. Solvent was removed in vacuo and the product was obtained by column chromatography on silica gel using a linear gradient of ethyl acetate in toluene.

4.6. General method for cyclization E

Dowex 50 in H^+ form (2 g/mmol) was added to the solution of **9** in dioxane (10 ml/mmol). The reaction mixture was heated to 90 °C for 3 h.

*4.6.1. 2-Nitrophenyl 3-ethoxyacryloylcarbamate (**7a**).* Ethoxyethylene (19 ml, 200 mmol) in dioxane (150 ml) was added to a solution of chlorocarbonylisocyanate (15 g, 142 mmol) in dioxane (200 ml) at 10 °C under an argon atmosphere during 20 min followed by triethylamine (20 ml, 142 mmol) in dioxane (150 ml) at 10 °C during 20 min (a white thick precipitate of triethylamine hydrochloride appeared). To this suspension, a solution of 2-nitrophenol (25 g, 180 mmol), [co-evaporated with toluene (2×100 ml) and dioxane (2×100 ml)], in dry dioxane (200 ml) was added at 10 °C under argon atmosphere during 30 min. The reaction mixture was stirred at 10 °C for 30 min, filtered under argon atmosphere, and the filtrate was concentrated in vacuo. The residue was triturated with 20% petroleum ether in toluene (250 ml). The yellowish crystals were immediately filtered off (under argon atmosphere), washed with 20% petroleum ether in toluene (2×50 ml) and then with petroleum ether (100 ml), and finally dried in vacuo over phosphorus pentoxide. The desired reagent **7a** was obtained in 57% yield (22.6 g, 80.65 mmol) in the form of yellowish crystals (mp 124.6 °C), ν_{max} ($CHCl_3$) 3400 (m), 3127 (w), 1808 (w, sh), 1783 (s), 1689 (s), 1621 (s, sh), 1605 (vs), 1534 (vs), 1490 (m), 1450 (s, sh), 1376 (m), 1350 (s), 1316 (m), 1251 (m), 1169 (vs), 1152 (vs), 1087 (s), 1023 (m), 980 (w, sh), 961 (m), 867 (w), 815 (w), 692 (m), 655 (w), 555 (vw), 508 (w), 448 (vw). δ_H (500.0 MHz, $CDCl_3$) 1.34 (3H, t, *J*(CH_3,CH_2)=7.1, CH_3), 3.98 (2H, qd, *J*(CH_2,CH_3)=7.1, *J*(CH_2,6)=0.5, O*C**H*$_2$CH$_3$), 6.36 (1H, d, *J*(5,6)=12.3, H-5), 7.35 (1H, dd, *J*(6′,5′)=8.2, *J*(6′,4′)=1.3, H-6′), 7.45 (1H, ddd, *J*(4′,3′)=8.2, *J*(4′,5′)=7.4, *J*(4′,6′)=1.3, H-4′), 7.69 (1H, ddd, *J*(5′,6′)=8.2, *J*(5′,4′)=7.4, *J*(5′,3′)=1.6, H-5′), 7.85 (1H, dt, *J*(6,5)=12.3, *J*(6,CH_2)=0.5, H-6), 8.13 (1H, dd, *J*(3′,4′)=8.2, *J*(3′,5′)=1.6, H-3′), 8.39 (1H, br s, H-3). δ_C (125.7 MHz, $CDCl_3$) 14.24 (CH_3), 67.31 (O*C**H*$_2$CH$_3$), 96.27 (C-5), 125.37 (C-6′), 125.88 (C-3′), 127.09 (C-4′), 134.87 (C-5′), 141.69 (C-2′), 143.15 (C-1′), 149.51 (C-2), 165.47 (C-6), 167.28 (C-4). For $C_{12}H_{12}N_2O_6$ (280.23) cald: 51.43% C, 4.32H, 10.00% N; found: 51.36% C, 4.33% H, 9.82% N. HRMS for $C_{12}H_{13}N_2O_6$ $(M+H)^+$ calcd 281.0768, found 281.0763.

*4.6.2. 2-Nitrophenyl 3-ethoxy-2-methylacryloylcarbamate (**7b**).* The title compound was prepared from 1-ethoxypropene (22 ml, 200 mmol) using the same procedure as for compound **7a** in 59% yield (24.66 g, 83.8 mmol) of yellowish crystals. Crystallization of the product **7b** proceeded in the refrigerator overnight (mp 139–143 °C), ν_{max}(KBr) 3293 (s), 3183 (w), 3104 (w), 3084 (w), 3048 (w), 1787 (vs), 1762 (s), 1678 (s), 1648 (s), 1621 (m), 1605 (m), 1605 (m), 1591 (m), 1533 (vs), 1524 (vs, sh), 1511 (s, sh), 1478 (s), 1450 (m), 1388 (m), 1369 (m, sh), 1352 (s), 1316 (m, sh), 1305 (s), 1211 (vs), 1184 (vs), 1160 (s), 1147 (s), 1122 (s), 1084 (s), 1026 (m), 975 (m), 959 (w, sh), 870 (w), 858 (w), 777 (m, sh), 761 (m), 747 (m), 704 (m), 688 (m), 629 (m), 559 (w), 435 (w). δ_H (600.1 MHz, $CDCl_3$) 1.33 (3H, t, *J*(CH_3,CH_2)=7.1, CH_3), 1.83 (3H, d, *J*(CH_3,6)=1.2, 5-CH_3), 4.09 (2H, q, *J*(CH_2,CH_3)=7.1, O*C**H*$_2$CH$_3$), 7.35 (1H, dd, *J*(6′,5′)=8.2, *J*(6′,4′)=1.3, H-6′), 7.42 (1H, ddd, *J*(4′,3′)=8.2, *J*(4′,5′)=7.4, *J*(4′,6′)=1.3, H-4′), 7.50 (1H, q, *J*(6,CH_3)=1.2, H-6), 7.67 (1H, ddd, *J*(5′,6′)=8.2, *J*(5′,4′)=7.4, *J*(5′,3′)=1.6, H-5′), 8.09 (1H, dd, *J*(3′,4′)=8.2, *J*(3′,5′)=1.6, H-3′), 8.17 (1H, br s, H-3). δ_C (150.9 MHz, $CDCl_3$) 9.10 (5-CH_3), 15.32 (*C**H*$_3$CH$_2$O), 70.44 (O*C**H*$_2$CH$_3$), 107.04 (C-5), 125.49 (C-6′), 125.76 (C-3′), 126.89 (C-4′), 134.85 (C-5′), 141.63 (C-2′), 143.26 (C-1′), 148.23 (C-2), 158.68 (C-6), 165.99 (C-4). Note: $CDCl_3$ must be made anhydrous by treating with K_2CO_3 and the NMR spectra must be measured as fast as possible because of the instability of the reagent!!

*4.6.3. 4-Nitrophenyl 3-ethoxyacryloylcarbamate (**7c**).* The title compound was prepared from 1-ethoxyethylene (19 ml, 200 mmol)

using the same procedure as for compound **7a** in 44% yield (17.5 g, 62.48 mmol) of light beige crystals. Crystallization of the product **7c** proceeded in the refrigerator overnight (mp 131.3 °C), ν_{max}(KBr) 3316 (m), 3266 (s), 3195 (m), 3116 (m), 3090 (m), 3060 (m), 3029 (w), 2996 (m), 2956 (w), 2912 (w), 2858 (w), 1802 (vs, sh), 1793 (vs), 1766 (m, sh), 1707 (m), 1691 (s), 1629 (vs, br), 1615 (vs, sh), 1595 (s), 1532 (vs, sh), 1516 (vs, br), 1491 (vs), 1473 (s, sh), 1450 (m), 1402 (m), 1362 (vs), 1354 (vs), 1331 (s), 1302 (m), 1259 (vs), 1207 (vs, sh), 1193 (vs, br), 1177 (s, sh), 1143 (vs, br), 1110 (s), 1107 (s), 1094 (m, sh), 1052 (w), 1021 (s), 978 (vs), 970 (s, sh), 954 (m), 871 (vs), 862 (vs), 749 (s), 719 (s), 678 (s), 633 (w), 529 (w), 494 (m). δ_H (500.0 MHz, $CDCl_3$) 1.37 (3H, t, $J(CH_3,CH_2)$=7.1, CH_3CH_3O), 4.02 (2H, qd, $J(CH_2,CH_3)$=7.1, $J(CH_2,6)$=0.5, OCH_2CH_3), 6.40 (1H, d, $J(5,6)$=12.3, H-5), 7.37 (2H, m, H-2′,6′), 7.87 (1H, dt, $J(6,5)$=12.3, $J(6,CH_2)$=0.6, H-6), 8.30 (2H, m, H-3′,5′), 8.34 (1H, br s, H-3). δ_C (125.7 MHz, $CDCl_3$) 14.28 (CH_3CH_2O), 67.51 (OCH_2CH_3), 96.23 (C-5), 122.33 (C-2′,6′), 125.12 (C-3′,5′), 145.50 (C-4′), 149.50 (C-2), 154.53 (C-1′), 165.67 (C-6), 167.37 (C-4). HRMS for $C_{12}H_{13}N_2O_6$ $(M+H)^+$ calcd 281.0768, found 281.0763.

*4.6.4. 4-Nitrophenyl 3-ethoxy-2-methylacryloylcarbamate (**7d**).* The title compound was prepared from 1-ethoxypropene (7.3 ml, 66.36 mmol) using the same procedure as for compound **7a** in 60% yield (8.43 g, 28.65 mmol) of white crystals. Crystallization of the product **7c** proceeded in the refrigerator overnight (mp 92.4 °C), ν_{max}(KBr) 3330 (m, br, sh), 3244 (m), 3173 (m), 3117 (m), 3083 (m), 3053 (w), 1824 (w), 1780 (vs), 1770 (vs), 1758 (s), 1677 (s, sh), 1661 (s), 1649 (vs), 1615 (m), 1592 (m), 1526 (vs, br), 1488 (vs), 1449 (m), 1388 (w), 1373(m), 1347 (vs), 1305 (s), 1227 (vs, sh), 1218 (vs), 1185 (vs, br), 1114 (vs), 1093 (m, sh), 863 (m, sh), 857 (s), 764 (m), 746 (m), 709 (m), 681 (m), 610–615 (w, br), 540 (w), 532 (w), 500 (w). δ_H (499.8 MHz, $CDCl_3$) 1.34 (3H, t, $J(CH_3,CH_2)$=7.1, CH_3CH_3O), 1.84 (3H, d, $J(CH_3,6)$=1.2, 5-CH_3), 4.10 (2H, q, $J(CH_2,CH_3)$=7.1, OCH_2CH_3), 7.33 (2H, m, H-2′,6′), 7.53 (1H, q, $J(6,CH_3)$=1.2, H-6), 8.24 (2H, m, H-3′,5′), 8.30 (1H, br s, H-3). δ_C (125.7 MHz, $CDCl_3$) 9.00 (5-CH_3), 15.25 (CH_3CH_2O), 70.54 (OCH_2CH_3), 106.95 (C-5), 122.10 (C-2′,6′), 125.12 (C-3′,5′), 145.25 (C-4′), 148.23 (C-2), 154.55 (C-1′), 158.82 (C-6), 166.29 (C-4). For $C_{13}H_{14}N_2O_6$ (294.09) calcd: 53.06% C, 4.80H, 9.52% N; found: 53.00% C, 4.80% H, 9.43% N.

*4.6.5. (3R)-3-Amino-1-N-Boc-pyrrolidine (**8a**).* A mixture of (3*S*)-1-*N*-Boc-3-mesyloxypyrrolidine[3] (4.87 g, 18.35 mmol) and sodium azide (6.5 g, 100 mmol) in DMF (150 ml) was stirred at 110 °C for 5 h. DMF was removed in vacuo and the crude azido derivative [HRMS for $C_9H_{16}N_4O_2$ $(M+Na)^+$ calcd 235.1165, found 235.1166] was purified using column chromatography on silica gel employing a linear gradient of ethyl acetate in toluene. The obtained azido derivative was dissolved in ethanol (200 ml) and on addition of Pd/C (0.4 g), it was hydrogenated at 10 psi overnight. Pd catalyst was filtered over Celite. Ethanol was then evaporated giving a 73% (2.5 g, 13.49 mmol) overall yield of title compound in the form of yellowish oil, which needed no further purification (NMR checking). ν_{max} ($CHCl_3$) 3379 (w), 3315 (w), 3165 (w, br), 2980 (vs), 1685 (vs, vbr), 1478 (s), 1455 (s), 1413 (vs, vbr), 1390 (vs, sh), 1367 (vs), 1249 (s), 1168 (vs, br), 1130 (vs, sh), 1123 (vs), 461 (w). δ_H (500.0 MHz, DMSO-d_6 mixture of two amidic isomers 1:1) 1.38 (18H, s, $(CH_3)_3C$), 1.51 and 1.85 (2×2H, 2×br m, H-4), 2.87 (2H, dd, J_{gem}=10.6, $J(2b,3)$=4.8, H-2b), 3.14–3.22 (2H, m, H-5b), 3.26–3.34 (4H, m, H-2a,5a), 3.37 and 3.38 (2×2H, 2×m, H-3). δ_C (125.7 MHz, DMSO-d_6, mixture of two amidic isomers 1:1) 28.44 (($\mathbf{C}H_3)_3C$), 33.64 and 34.39 (C-4), 44.26 and 44.47 (C-5), 50.30 and 51.18 (C-3), 54.06 and 54.35 (C-2), 78.20 ($\mathbf{C}(CH_3)_3$), 153.85 and 153.90 (CO). HRMS for $C_9H_{19}N_2O_2$ $(M+H)^+$ calcd 187.1441, found 187.1439.

*4.6.6. (3S,4R)-4-Amino-1-N-Boc-3-dimethoxytrityloxypyrrolidine (**8b**).* A mixture of (3*S*,4*S*)-1-*N*-Boc-4-dimethoxytrityloxy-3-mesyloxypyrrolidine[4] (8 g, 13.69 mmol) and sodium azide (4.3 g, 66 mmol) in DMF (130 ml) was stirred at 110 °C for 5 h. DMF was removed in vacuo, the residue was dissolved in ethyl acetate, and the solution filtered through a pad of Celite and finally submitted to flash chromatography on silica gel using linear gradient of ethyl acetate in toluene. The obtained crude azido derivative was dissolved, without further purification in ethanol (200 ml), the Pd/C catalyst (0.4 g) was added, and the whole was hydrogenated at 10 psi for 6 h. The catalyst was then filtered off using Celite, ethanol was evaporated, and the title compound was obtained by column chromatography on silica gel using a linear gradient of ethanol in chloroform in 72% yield (4.98 g, 9.87 mmol) in the form of white foam. ν_{max}(KBr) 3057 (w), 3036 (w), 3000 (w), 2972 (m), 2836 (w), 1695 (vs), 1608 (m), 1582 (w), 1509 (s), 1492 (w, sh), 1477 (w), 1463 (m), 1456 (m), 1446 (m), 1408 (s), 1391 (m, sh), 1365 (m), 1302 (m), 1252 (s), 1177 (s), 1155 (m, sh), 1117 (w), 1088 (s), 1034 (m), 1015 (w, sh), 1000 (w), 912 (w), 829 (m), 755 (w), 702 (w), 627 (w). δ_H (500.0 MHz, DMSO-d_6 mixture of two amidic isomers 1:1) 1.28 and 1.32 (2×9H, 2×s, $(CH_3)_3C$), 2.44 (1H, dd, J_{gem}=10.8, $J(2b,3)$=6.6, H-2b), 2.64 (1H, dd, J_{gem}=10.8, $J(2a,3)$=7.3, H-2a), 2.71 (1H, m, H-4), 2.72 (1H, dd, J_{gem}=10.9, $J(2b,3)$=7.2, H-2b), 2.86 (1H, dd, J_{gem}=10.8, $J(2a,3)$=7.8, H-2a), 2.90–2.99 (3H, m, H-4 and 2×H-5b), 3.02–3.07 (2H, m, 2×H-5a), 3.73 (12H, s, CH_3O-DMTr), 3.83 (1H, ddd, $J(3,2)$=7.3, 6.6, $J(3,4)$=4.4, H-3), 3.86 (1H, ddd, $J(3,2)$=7.8, 7.2, $J(3,4)$=4.6, H-3), 6.90 (8H, m, H-*m*-C_6H_4-DMTr), 7.23 (2H, m, H-*p*-C_6H_5-DMTr), 7.29–7.36 (12H, m, H-*o*-C_6H_4-DMTr and H-*m*-C_6H_5-DMTr), 7.44 and 7.47 (2×2H, 2×m, H-*o*-C_6H_5-DMTr). δ_C (125.7 MHz, DMSO-d_6, mixture of two amidic isomers 1:1) 28.26 and 28.35 (($\mathbf{C}H_3)C$), 47.64 and 47.95 (C-2), 51.32 (C-5), 51.75 (C-4), 51.89 (C-5), 52.04 (C-4), 55.27 and 55.29 (CH_3O-DMTr), 73.21 and 73.72 (C-3), 78.17 and 78.36 ($\mathbf{C}(CH_3)_3$), 86.17 (C-DMTr), 113.57 (C-*m*-C_6H_4-DMTr), 126.96 and 127.04 (C-*p*-C_6H_5-DMTr), 127.79 and 127.86 (C-*o*-C_6H_5-DMTr), 128.19 (C-*m*-C_6H_5-DMTr), 129.94, 129.99 and 130.05 (C-*o*-C_6H_4-DMTr), 136.30, 136.51 and 136.64 (C-*i*-C_6H_4-DMTr), 145.79 and 145.83 (C-*i*-C_6H_5-DMTr), 153.71 and 153.82 (CO), 158.44 and 158.53 (C-*p*-C_6H_4-DMTr). HRMS for $C_{30}H_{36}N_2O_5Na$ $(M+Na)^+$ calcd 527.2516, found 527.2512.

*4.6.7. (3S,4S)-4-Amino-1-N-Boc-3-dimethoxytrityloxypyrrolidine (**8c**).* A mixture of (3*R*,4*S*)-1-*N*-Boc-4-dimethoxytrityloxy-3-mesyloxypyrrolidine[4] (4.28 g, 7.33 mmol) and sodium azide (2.38 g, 37 mmol) in DMF (80 ml) was stirred at 110 °C for 5 h. DMF was removed in vacuo, and the residue was dissolved in ethyl acetate and filtered through a pad of Celite followed by purification on silica gel using a linear gradient of ethyl acetate in toluene. The obtained crude azido derivative was dissolved in ethanol (200 ml), Pd/C (0.2 g) was added, and the whole was hydrogenated for 6 h. The catalyst was filtered off over Celite, ethanol was evaporated, and the title compound was recovered using column chromatography on silica gel under linear gradient of ethanol in chloroform in a 68% yield (2.53 g, 5.01 mmol) in the form of white foam. ν_{max}(KBr) 3382 (w), 3322 (w), 3057 (w), 3036 (w), 3000 (w), 2973 (m), 2836 (w), 1736 (m), 1694 (vs), 1608 (s), 1582 (w), 1509 (vs), 1491 (m, sh), 1478 (m), 1463 (m), 1456 (m), 1446 (m), 1408 (vs), 1392 (s, sh), 1365 (m), 1301 (m), 1252 (vs), 1175 (vs), 1155 (s, sh), 1114 (s), 1034 (s), 1009 (m), 1002 (w, sh), 912 (w), 828 (s), 770 (m), 754 (m), 702 (m), 627 (w). δ_H (500.0 MHz, DMSO-d_6 mixture of two amidic isomers 1:1) 1.29 and 1.37 (2×9H, 2×s, $(CH_3)_3C$), 2.39 (1H, dd, J_{gem}=11.7, $J(2b,3)$=2.4, H-2b), 2.65 (1H, dd, J_{gem}=11.7, $J(2b,3)$=1.9, H-2b), 2.77 (1H, dd, J_{gem}=11.7, $J(2a,3)$=4.8, H-2a), 2.87 (1H, dd, J_{gem}=10.9, $J(5b,4)$=3.0, H-5b), 2.89 (1H, dt, $J(4,5)$=5.0, 2.5, $J(4,3)$=2.5, H-4), 2.92 (1H, dd, J_{gem}=10.5, $J(5b,4)$=2.5, H-5b), 2.96 (1H, dd, J_{gem}=11.7, $J(2a,3)$=4.9, H-2a), 3.01 (1H, dt, $J(4,5)$=5.6, 3.0, $J(4,3)$=3.0, H-4), 3.37 (1H, dd, J_{gem}=10.9, $J(5a,4)$=5.6, H-5a), 3.39 (1H, dd, J_{gem}=10.5, $J(5a,4)$=5.0, H-5a), 3.69 (1H, ddd, $J(3,2)$=4.8, 2.4, $J(3,4)$=3.0, H-3), 3.71 (1H, ddd, $J(3,2)$=4.9, 1.9, $J(3,4)$=2.5, H-3), 3.730, 3.732 and

3.736 (12H, 3×s, CH_3O-DMTr), 6.90 (8H, m, H-*m*-C_6H_4-DMTr), 7.20–7.33 (14H, m, H-*o*-C_6H_4-DMTr and H-*m*,*p*-C_6H_5-DMTr), 7.39 and 7.42 (2×2H, 2×m, H-*o*-C_6H_5-DMTr). δ_C (125.7 MHz, DMSO-d_6, mixture of two amidic isomers 1:1) 28.27 and 28.40 (($\mathbf{C}H_3$)C), 50.28 and 50.49 (C-2), 51.77 and 52.27 (C-5), 55.25 (CH_3O-DMTr), 55.58 and 56.53 (C-4), 77.98 (C-3), 78.10 and 78.34 ($\mathbf{C}(CH_3)_3$), 78.50 (C-3), 86.18 and 86.28 (C-DMTr), 113.48 and 113.51 (C-*m*-C_6H_4-DMTr), 126.94 and 127.01 (C-*p*-C_6H_5-DMTr), 127.99 and 128.12 (C-*o*,*m*-C_6H_5-DMTr), 130.15 (C-*o*-C_6H_4-DMTr), 136.32, 136.49 and 136.60 (C-*i*-C_6H_4-DMTr), 145.80 (C-*i*-C_6H_5-DMTr), 153.93 and 153.95 (CO), 158.39, 158.47 and 158.48 (C-*p*-C_6H_4-DMTr). HRMS for $C_{30}H_{36}N_2O_5Na$ $(M+Na)^+$ calcd 527.2516, found 527.2512.

*4.6.8. 1-((3R)-1-N-Boc-3-Pyrrolidinyl)-3-(3-ethoxyacryloyl)urea (**9a**).* The title compound was prepared according to general method A from compound **8a** (1.15 g, 6.2 mmol) using reagent **7a**.Yield, 85% (1.72 g, 5.254 mmol) of yellowish foam. ν_{max}($CHCl_3$) 3428 (w), 3268 (w, br, sh), 3236 (w), 3132 (w, sh), 3102 (w), 2983 (m), 1700 (s, sh), 1685 (vs, sh), 1676 (vs), 1624 (s), 1611 (s), 1548 (s), 1498 (m, sh), 1487 (m), 1476 (m), 1456 (m), 1412 (s), 1395 (s, sh), 1368 (m), 1248 (m), 1167 (s), 1132 (s), 977 (w), 960 (w), 846 (w). δ_H (500.0 MHz, $CDCl_3$, mixture of two amidic isomers 1:1) 1.36 (6H, t, J(CH_3,CH_2)=7.1, CH_3), 1.46 (18H, s, $(CH_3)_3C$), 1.89 (2H, br m, H-4′b), 2.17 (2H, dddd, J_{gem}=13.2, J(4′a,5′)=7.8, 5.9, J(4′a,3′)=6.3, H-4′a), 3.21 and 3.30 (2×1H, 2×bdd, J_{gem}=10.9, J(2′b,3′)=5.0, H-2′b), 3.39–3.70 (4H, br m, H-5′), 3.63–3.70 (2H, br m, H-2′a), 3.98 (4H, q, J(CH_2,CH_3)=7.1, OCH_2CH_3), 4.39 (2H, m, H-3′), 5.32 (2H, d, J(5,6)=12.2, H-5), 7.63 (2H, d, J(6,5)=12.2, H-6), 8.84 (2H, br d, J(1,3′)=7.0, H-1), 9.27 and 9.40 (2×1H, 2×br s, H-3). δ_C (125.7 MHz, $CDCl_3$, mixture of two amidic isomers 1:1) 14.50 (CH_3), 28.46 (($\mathbf{C}H_3$)$_3$C), 31.07 and 31.81 (C-4′), 43.74 and 44.07 (C-5′), 48.97 and 49.69 (C-3′), 51.25 and 51.57 (C-2′), 67.68 (OCH_2CH_3), 79.49 ($\mathbf{C}(CH_3)_3$), 97.82 (C-5), 154.42 and 154.82 (C-2 and CO), 162.93 and 163.04 (C-6), 168.17 (C-4). HRMS for $C_{15}H_{25}N_3O_5Na$ $(M+Na)^+$ calcd 350.1686, found 350.1687.

*4.6.9. 1-((3S,4R)-1-N-Boc-3-Dimethoxytrityloxy-4-pyrrolidinyl)-3-(3-ethoxyacryloyl)urea (**9b**).* The title compound was prepared according to general method A from compound **8b** (0.95 g, 1.88 mmol) and reagent **7a** in 93% yield (1.13 g, 1.13 mmol) of yellowish foam. ν_{max}(KBr) 3261 (w, br), 3101 (w, br), 2976 (m), 2837 (w), 1701 (vs), 1679 (vs), 1628 (m, sh), 1610 (s), 1577 (w, sh), 1540 (s, br), 1510 (vs), 1492 (m, sh), 1477 (m), 1465 (m, sh), 1446 (m), 1404 (s), 1393 (m, sh), 1366 (m), 1303 (m), 1252 (s), 1222 (m, sh), 1176 (s), 1176 (s), 1093 (m), 1035 (m), 1017 (m, sh), 978 (w), 913 (vw), 829 (m), 771 (w), 701 (w). δ_H (500.0 MHz, $CDCl_3$, mixture of two amidic isomers 1:1) 1.36 (6H, t, J(CH_3,CH_2)=7.1, CH_3), 1.46 (18H, s, $(CH_3)_3C$), 2.75 (1H, dd, J_{gem}=11.6, J(2′b,3′)=7.2, H-2′b), 2.88 (1H, dd, J_{gem}=11.6, J(2′a,3′)=7.7, H-2′a), 3.16 (1H, dd, J_{gem}=11.6, J(2′b,3′)=7.7, H-2′b), 3.22–3.32 (3H,. m, H-2′a and 2×5′b), 3.46 (1H, br m, H-4′), 3.49 and 3.54 (2×1H, 2×dd, J_{gem}=11.8, J(5′a,4′)=2.8, H-5′a), 3.75 and 3.76 (2×6H, 2×s, CH_3O-DMTr), 3.80 (1H, br m, H-4′), 3.917 and 3.923 (2×2H, 2×q, J(CH_2,CH_3)=7.1, OCH_2CH_3), 4.12 and 4.15 (2×1H, 2×br m, H-3′), 5.27 and 5.31 (2×1H, 2×d, J(5,6)=12.1, H-5), 6.81 and 6.83 (2×4H, 2×m, H-*m*-C_6H_4-DMTr), 7.20 (2H, m, H-*p*-C_6H_5-DMTr), 7.28 (4H, br m, H-*m*-C_6H_5-DMTr), 7.40 (8H, br m, H-*o*-C_6H_4-DMTr), 7.50 and 7.52 (2×2H, 2×m, H-*o*-C_6H_5-DMTr), 7.67 (2H, d, J(6,5)=12.1, H-6), 9.03 (1H, br s, H-3), 9.28 (2H, br d, J(1,4′)=5.6, H-1), 9.31 (1H, br s, H-3). δ_C (125.7 MHz, $CDCl_3$, mixture of two amidic isomers 1:1) 14.50 (CH_3), 28.32 and 28.37 (($\mathbf{C}H_3$)C), 48.52 and 48.81 (C-2′), 49.47 and 50.34 (C-5′), 51.27 and 51.74 (C-4′), 55.16 (CH_3O-DMTr), 67.42 and 67.50 (OCH_2CH_3), 71.28 and 71.80 (C-3′), 79.26 and 79.41 ($\mathbf{C}(CH_3)_3$), 87.08 and 87.15 (C-DMTr), 97.92 and 97.99 (C-5), 113.24 (C-*m*-C_6H_4-DMTr), 126.96 and 127.04 (C-*p*-C_6H_5-DMTr), 127.99 (C-*m*-C_6H_5-DMTr), 128.04 and 128.14 (C-*o*-C_6H_5-DMTr), 129.97 and 130.01 (C-*o*-C_6H_4-DMTr), 136.06, 136.17 and 136.22 (C-*i*-C_6H_4-DMTr), 144.87 and 144.95 (C-*i*-C_6H_5-DMTr), 154.08 and 154.23 (CO), 155.07 and 155.14 (C-2), 158.67 and 158.72 (C-*p*-C_6H_4-DMTr), 162.70 and 162.81 (C-6), 167.50 and 167.80 (C-4). HRMS for $C_{36}H_{43}N_3O_8Na$ $(M+Na)^+$ calcd 668.2942, found 668.2942.

*4.6.10. 1-((3S,4S)-1-N-Boc-3-Dimethoxytrityloxy-4-pyrrolidinyl)-3-(3-ethoxyacryloyl)urea (**9c**).* The title compound was prepared according to general method A from compound **8c** (0.9 g, 1.84 mmol) and reagent **7a** in 78% yield (1.04 g, 1.612 mmol) of yellowish foam. ν_{max}(KBr) 3416 (w, vbr), 3261 (w, br), 3089 (w, br), 2976 (m), 2837 (w), 1699 (vs), 1681 (vs), 1628 (m, sh), 1610 (s), 1578 (w, sh), 1549 (s, br), 1509 (s), 1492 (m, sh), 1475 (m), 1466 (m), 1446 (m), 1404 (m, br), 1394 (m, sh), 1367 (m), 1303 (m), 1251 (s), 1174 (s), 1111 (m, sh), 1089 (m), 1035 (m), 1018 (w, sh), 976 (w), 913 (vw), 829 (m), 769 (w), 756 (w), 703 (w), δ_H (500.0 MHz, $CDCl_3$, mixture of two amidic isomers 1:1) 1.33 (6H, t, J(CH_3,CH_2)=7.1, CH_3), 1.36 and 1.42 (2×9H, 2×s, $(CH_3)_3C$), 2.48 (1H, dd, J_{gem}=12.3, J(2′b,3′)=3.4, H-2′b), 2.66 (1H, dd, J_{gem}=12.3, J(2′a,3′)=5.3, H-2′a), 2.91 (1H, dd, J_{gem}=12.2, J(2′b,3′)=4.2, H-2′b), 2.99 (1H, dd, J_{gem}=12.2, J(2′a,3′)=5.9, H-2′a), 3.19 (1H, dd, J_{gem}=11.7, J(5′b,4′)=4.8, H-5′b), 3.24 (1H, dd, J_{gem}=11.4, J(5′b,4′)=4.5, H-5′b), 3.70 (1H, dd, J_{gem}=11.7, J(5′a,4′)=6.1, H-5′a), 3.75 and 3.76 (2×6H, 2×s, CH_3O-DMTr), 3.78 (1H, dd, J_{gem}=11.4, J(5′a,4′)=6.4, H-5′a), 3.96 (4H, q, J(CH_2,CH_3)=7.1, OCH_2CH_3), 4.03–4.13 (2H, br m, H-3′), 4.20 and 4.36 (2×1H, 2×br m, H-4′), 5.33 and 5.35 (2×1H, 2×d, J(5,6)=12.2, H-5), 6.80 and 6.82 (2×4H, 2×br m, H-*m*-C_6H_4-DMTr), 7.15–7.22 (2H, m, H-*p*-C_6H_5-DMTr), 7.23–7.29 (4H, m, H-*m*-C_6H_5-DMTr), 7.31–7.38 (8H, m, H-*o*-C_6H_4-DMTr), 7.44 and 7.46 (2×2H, 2×m, H-*o*-C_6H_5-DMTr), 7.63 (2H, d, J(6,5)=12.1, H-6), 8.68 and 8.77 (2×1H, 2×br d, J(1,4′)=8.2, H-1), 9.33 and 9.47 (2×1H, 2×br s, H-3). δ_C (125.7 MHz, $CDCl_3$, mixture of two amidic isomers 1:1) 14.49 (CH_3), 28.30 and 28.41 (($\mathbf{C}H_3$)C), 48.86 and 49.39 (C-5′), 50.13 (C-2′), 54.54 (C-4′), 55.13 and 55.14 (CH_3O-DMTr), 67.68 and 67.74 (OCH_2CH_3), 75.40 and 76.08 (C-3′), 79.24 and 79.47 ($\mathbf{C}(CH_3)_3$), 86.95 and 87.03 (C-DMTr), 97.81 (C-5), 113.24 and 113.28 (C-*m*-C_6H_4-DMTr), 126.96 and 127.01 (C-*p*-C_6H_5-DMTr), 127.92 (C-*m*-C_6H_5-DMTr), 128.10 and 128.24 (C-*o*-C_6H_5-DMTr), 130.10 and 130.13 (C-*o*-C_6H_4-DMTr), 136.00, 136.17 and 136.36 (C-*i*-C_6H_4-DMTr), 145.04 (C-*i*-C_6H_5-DMTr), 154.20, 154.38 and 154.58 (C-2 and CO), 158.67 and 158.73 (C-*p*-C_6H_4-DMTr), 162.97 (C-6), 167.95 and 168.11 (C-4). HRMS for $C_{36}H_{43}N_3O_8Na$ $(M+Na)^+$ calcd 668.2942, found 668.2941.

*4.6.11. 1-Cyclopentyl-3-(3-ethoxyacryloyl)urea (**9d**).* The title compound was prepared according to general method A from compound **8d** (0.2 g, 2.348 mmol) and reagent **7a** in 88% yield (0.47 g, 2.079 mmol) of white solid. ν_{max}(KBr) 3422 (w, vbr), 3258 (m), 3235 (m), 3133 (w, sh), 3103 (m), 2985 (m, sh), 2962 (m), 2940 (m, sh), 2869 (w), 1695 (s, sh), 1681 (vs), 1613 (s), 1550 (vs), 1501 (m), 1453 (w), 1473 (m), 1396 (w), 1367 (w), 1326 (w), 1242 (m), 1166 (s), 973 (w). δ_H (600.1 MHz, DMSO-d_6) 1.24 (3H, t, J(CH_3,CH_2)=7.0, CH_3), 1.38 (2H, m, H-2′a and H-5′a), 1.50–1.65 (4H, m, H-3′ and H-4′), 1.84 (2H, m, H-2′b and H-5′b), 3.93 (2H, q, J(CH_2,CH_3)=7.0, OCH_2CH_3), 3.98 (1H, m, H-1′), 5.49 (1H, d, J(5,6)=12.3, H-5), 7.54 (1H, d, J(6,5)=12.3, H-6), 8.52 (1H, br d, J(1,1′)=7.2, H-1), 10.00 (1H, br s, H-3). δ_C (150.9 MHz, DMSO-d_6) 14.68 (CH_3), 23.39 (C-3′ and C-4′), 32.97 (C-2′ and C-5′), 50.93 (C-1′), 67.52 (OCH_2CH_3), 98.57 (C-5), 153.54 (C-2), 162.32 (C-6), 168.15 (C-4). HRMS for $C_{11}H_{18}N_2O_3Na$ $(M+Na)^+$ calcd 249.1210, found 249.1210.

*4.6.12. 1-Cyclohexyl-3-(3-ethoxyacryloyl)urea (**9e**).* The title compound was prepared according to general method A from compound **8e** (0.233 g, 2.348 mmol) and reagent **7a** in 88% yield (0.5 g, 2.08 mmol) of white solid. ν_{max}(KBr) 3382 (w, vbr), 3256 (m), 3237 (m), 3095 (m), 3060 (m), 2984 (m), 2977 (m), 2938 (s), 2930 (s),2853 (m), 1698 (s), 1681 (vs), 1613 (vs), 1550 (vs), 1499 (m), 1473

(m), 1394 (w), 1446 (m), 1367 (w), 1326 (m), 1317 (m), 1252 (m), 1242 (s), 1227 (m), 1168 (vs), 998 (m), 955 (w). δ_H (500.0 MHz, DMSO-d_6) 1.24(3H, t, J(CH_3,CH_2)=7.0, CH_3), 1.16–1.35 (5H, m, H-2′ax, 3′ax, 4′ax, 5′ax and H-6′ax), 1.51 (1H, m, H-4′eq), 1.61 (2H, m, H-3′eq and H-5′eq), 1.78 (2H, m, H-2′eq and H-6′eq), 3.55 (1H, m, H-1′), 3.94 (2H, q, J(CH_2,CH_3)=7.1, OCH_2CH_3), 5.49 (1H, d, J(5,6)=12.3, H-5), 7.55 (1H, d, J(6,5)=12.3, H-6), 8.52 (1H, br d, J(1,1′)=7.6, H-1), 10.00 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 14.60 (CH_3), 24.25 (C-4′), 25.29 (C-3′ and C-5′), 32.58 (C-2′ and C-6′), 47.63 (C-1′), 67.45 (OCH_2CH_3), 98.57 (C-5), 153.11 (C-2), 162.20 (C-6), 168.07 (C-4). HRMS for $C_{12}H_{20}N_2O_3Na$ $(M+Na)^+$ calcd 263.1366, found 263.1366.

*4.6.13. 1-(Ethoxyacryloyl)-3-(trans-2-hydroxycyclohexyl)urea (**9f**).* The title compound was prepared according to general method C from compound **8f** (0.197 g, 1.3 mmol) and reagent **7a** in 99% yield (0.33 g, 1.287 mmol) of white solid. ν_{max}(KBr) 3512 (m), 3379 (m, vbr), 3260 (s, vbr), 3135 (m), 3096 (m), 2975 (m), 2936 (s), 2859 (s), 1702 (vs), 1672 (vs, br), 1643 (s, sh), 1620 (vs), 1610 (vs), 1565 (vs, br), 1489 (m), 1474 (m), 1450 (m), 1397 (m), 1372 (w), 1327 (s, sh), 1318 (s), 1252 (s), 1235 (s), 1170 (vs), 1042 (m), 977 (m). δ_H (499.8 MHz, DMSO-d_6) 1.07–1.28 (4H, m, H-3′ax, 4′ax, 5′ax and H-6′ax), 1.24 (3H, t, J(CH_3,CH_2)=7.1, CH_3), 1.52 (1H, m, H-5′eq), 1.60 (1H, m, H-4′eq), 1.80 (1H, m, H-6′eq), 1.95 (1H, m, H-3′eq), 3.23 (1H, m, H-1′), 3.35 (1H, m, H-2′), 3.94 (2H, q, J(CH_2,CH_3)=7.1, OCH_2CH_3), 4.75 (1H, d, J(OH,1′)=5.4, OH), 5.50 (1H, d, J(5,6)=12.4, H-5), 7.54 (1H, d, J(6,5)=12.4, H-6), 8.56 (1H, br d, J(1,2′)=7.4, H-1), 9.97 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 14.58 (CH_3), 23.58 (C-5′), 24.01 (C-4′), 30.99 (C-3′), 34.07 (C-6′), 54.60 (C-2′), 67.37 (OCH_2CH_3), 71.25 (C-1′), 98.64 (C-5), 153.82 (C-2), 162.01 (C-6), 167.87 (C-4). HRMS for $C_{12}H_{20}N_2O_4Na$ $(M+Na)^+$ calcd 279.1315, found 279.1316.

*4.6.14. 1-(3-Ethoxyacryloyl)-3-(cis-2-hydroxycyclopentyl)urea (**9g**).* The title compound was prepared according to general method C from compound **8g** (0.179 g, 1.3 mmol) and reagent **7a** in 95% yield (0.30 g, 1.238 mmol) of white solid. ν_{max}(KBr) 3435 (s, br), 3293 (m), 3237 (m, br), 3141 (m), 3096 (m), 2983 (m), 2964 (m), 2942 (m), 2872 (w), 1698 (vs), 1676 (vs), 1610 (vs), 1535 (s), 1486 (s), 1474 (m), 1458 (m), 1395 (w), 1368 (w, sh), 1322 (m), 1246 (m), 1185 (s), 1163 (s), 1014 (m), 973 (m). δ_H (499.8 MHz, DMSO-d_6) 1.24 (3H, t, J(CH_3,CH_2)=7.0, CH_3), 1.40–1.48 (2H, m, H-3′a and H-4′a), 1.54 (1H, m, H-5′a), 1.66–1.80 (2H, m, H-4′b and H-5′b), 1.84 (1H, m, H-3′b), 3.80 (1H, m, H-2′), 3.92 (1H, m, H-1′), 3.94 (2H, q, J(CH_2,CH_3)=7.0, OCH_2CH_3), 4.89 (1H, d, J(OH,1′)=4.5, OH), 5.51 (1H, d, J(5,6)=12.3, H-5), 7.53 (1H, d, J(6,5)=12.3, H-6), 8.72 (1H, br d, J(1,2′)=7.9, H-1), 9.92 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 14.59 (CH_3), 20.22 (C-4′), 29.51 (C-3′), 32.73 (C-5′), 54.05 (C-2′), 67.33 (OCH_2CH_3), 70.85 (C-1′), 98.69 (C-5), 153.58 (C-2), 161.91 (C-6), 167.56 (C-4). HRMS for $C_{11}H_{18}N_2O_4Na$ $(M+Na)^+$ calcd 265.1159, found 265.1159.

*4.6.15. (RS)-1-(3-(3-Ethoxyacryloyl)ureido)-1-hydroxymethtylcyclopentane **9h**.* The title compound was prepared according to general method A from compound **8h** (0.27 g, 2.348 mmol) and reagent **7a** in 88% yield (0.53 g, 2.069 mmol) of white solid. ν_{max}(KBr) 3415 (m, br), 3273 (m, br, sh), 3220 (m, br), 3127 (m), 3093 (m), 3065 (w), 2980 (m, sh), 2965 (m), 2879 (w), 1701 (m, sh), 1677 (vs), 1610 (s), 1567 (s, sh), 1556 (s), 1488 (m), 1473 (m), 1448 (w), 1396 (w), 1373 (w), 1328 (m), 1246 (m), 1179 (s), 1156 (s), 990 (w, sh). δ_H (600.1 MHz, DMSO-d_6) 1.24 (3H, t, J(CH_3,CH_2)=7.0, CH_3), 1.52 (2H, m, H-3′a and H-4′a), 1.61–1.67 (4H, m, H-3′b, 4′b, 2′a and H-5′a), 1.77 (2H, m, H-2′b and H-5′b), 3.43 (2H, d, J(CH_2,OH)=5.5, CH_2OH), 3.93 (2H, q, J(CH_2,CH_3)=7.0, OCH_2CH_3), 4.90 (1H, t, J(OH,CH_2)=5.5, OH), 5.50 (1H, d, J(5,6)=12.3, H-5), 7.53 (1H, d, J(6,5)=12.3, H-6), 8.64 (1H, br s, H-1), 9.85 (1H, br s, H-3). δ_C (150.9 MHz, DMSO-d_6) 14.65 (CH_3), 24.21 (C-3′ and C-4′), 34.39 (C-2′ and C-5′), 64.63 (C-1′), 64.88 (CH_2OH), 67.42 (OCH_2CH_3), 98.67 (C-5), 153.06 (C-2), 162.07 (C-6), 168.01 (C-4). HRMS for $C_{12}H_{20}N_2O_4Na$ $(M+Na)^+$ calcd 279.1315, found 279.1316.

*4.6.16. 1-(2,3-Dihydroxypropyl)-3-(3-ethoxy-2-methylacryloyl)urea (**9i**).* The title compound was prepared according to general method A from compound **8i** (0.118 g, 1.3 mmol) and reagent **7a** in 87% yield (0.26 g, 1.12 mmol) of white solid. ν_{max}(KBr) 3304 (s), 3237 (s, br, sh), 3145 (s, br, sh), 2984 (m), 1688 (vs), 1635 (m, sh), 1609 (vs), 1545 (vs), 1500 (m), 1476 (m), 1394 (w), 1365 (m), 1332 (m), 1250 (s), 1225 (m), 1162 (vs), 1095 (s), 1063 (s), 972 (m). δ_H (500.0 MHz, DMSO-d_6) 1.24 (3H, t, J(CH_3,CH_2)=7.0, CH_3), 3.02 (1H, m, H-1′a), 3.24 (1H, m, H-3′a), 3.31–3.38 (2H, m, H-1′b and H-3′b), 3.50 (1H, m, H-2′), 3.94 (2H, q, J(CH_2,CH_3)=7.0, OCH_2CH_3), 4.65 (1H, t, J(OH,3′)=5.6, 3′-OH), 4.90 (1H, d, J(OH,2′)=5.0, 2′-OH), 5.50 (1H, d, J(5,6)=12.3, H-5), 7.55 (1H, d, J(6,5)=12.3, H-6), 8.63 (1H, bt, J(1,1′)=5.3, H-1), 10.01 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 14.63 (CH_3), 42.50 (C-1′), 63.88 (C-3′), 67.44 (OCH_2CH_3), 70.27 (C-2′), 98.63 (C-5), 154.20 (C-2), 162.13 (C-6), 167.76 (C-4). HRMS for $C_9H_{16}N_2O_5Na$ $(M+Na)^+$ calcd 255.0951, found 255.0952.

*4.6.17. 1-(3-Ethoxyacryloyl)-3-phenylurea (**9j**).* The title compound was prepared according to general method A from compound **8j** (0.091 ml, 1 mmol) and reagent **7a** in 94% yield (0.22 g, 0.94 mmol) of white solid. ν_{max}(KBr) 3404 (w, br), 3242 (w), 3230 (w, br), 3132 (m, br), 3096 (m), 3063 (m), 3029 (w), 2980 (m), 2936 (w), 1710 (s), 1682 (vs), 1673 (s, sh), 1621 (vs), 1607 (s, sh), 1597 (vs), 1560 (vs), 1500 (m), 1495 (m, sh), 1472 (w), 1448 (m), 1393 (w), 1367 (vw), 1305 (w, sh), 1262 (m), 1245 (s), 1230 (m), 1159 (vs), 1084 (vw), 1018 (w), 1002 (w), 987 (w), 847 (w), 758 (m), 689 (w), 616 (vw), 512 (w). δ_H (500.0 MHz, $CDCl_3$) 1.38 (3H, t, J(CH_3,CH_2)=7.1, CH_3), 3.98 (2H, q, J(CH_2,CH_3)=7.1, OCH_2CH_3), 5.43 (1H, d, J(5,6)=12.3, H-5), 7.11 (1H, m, H-*p*-Ph), 7.31 (2H, m, H-*m*-Ph), 7.55 (2H, m, H-*o*-Ph), 7.73 (1H, d, J(6,5)=12.3, H-6), 9.61 and 10.85 (2×1H, 2×br s, H-1,3). δ_C (125.7 MHz, $CDCl_3$) 14.41 (CH_3), 67.22 (OCH_2CH_3), 97.65 (C-5), 120.31 (C-*o*-Ph), 124.16 (C-*p*-Ph), 128.87 (C-*m*-Ph), 137.39 (C-*i*-Ph), 152.86 (C-2), 163.18 (C-6), 168.39 (C-4). HRMS for $C_{12}H_{14}N_2O_3Na$ $(M+Na)^+$ calcd 257.0897, found 257.0894.

*4.6.18. Methyl 2-(3-(3-ethoxyacryloyl)ureido)acetate (**9k**).* The title compound was prepared according to general method C from compound **8k** (0.5 g, 3.98 mmol) and reagent **7a** in 87% yield (0.8 g, 3.475 mmol) of white solid. ν_{max}(KBr) 3387 (w, vbr), 3309 (m, br), 3238 (m, br), 3138 (m, sh), 3111 (m), 3095 (m, sh), 2984 (m), 1749 (vs), 1702 (vs), 1686 (s), 1673 (vs), 1616 (vs), 1570 (vs), 1504 (m), 1476 (w), 1437 (m), 1401 (m), 1385 (w), 1180 (vs), 983 (w). δ_H (500.0 MHz, $CDCl_3$) 1.36 (3H, t, J(CH_3,CH_2)=7.0, CH_3), 3.76 (3H, s, CH_3O), 3.97 (2H, q, J(CH_2,CH_3)=7.0, OCH_2CH_3), 4.09 (2H, d, J(CH_2,1)=5.6, CH_2), 5.34 (1H, d, J(5,6)=12.2, H-5), 7.66 (1H, d, J(6,5)=12.2, H-6), 9.10 (1H, bt, J(1,CH_2)=5.6, H-1), 9.66 (1H, br s, H-3). δ_C (125.7 MHz, $CDCl_3$) 14.46 (CH_3), 41.53 (CH_2), 52.28 (CH_3O), 67.49 (OCH_2CH_3), 97.90 (C-5), 155.51 (C-2), 162.99 (C-6), 168.13 (C-4), 169.86 (COO). HRMS for $C_9H_{14}N_2O_5Na$ $(M+Na)^+$ calcd 253.0795, found 253.0793.

*4.6.19. Ethyl 2(R)-(3-(3-ethoxyacryloyl)ureido)propanoate (**9l**).* The title compound was prepared according to general method C from compound **8l** (0.5 g, 3.25 mmol) and reagent **7a** in 87% yield (0.73 g, 2.83 mmol) of white solid. ν_{max}(KBr) 3375 (m, sh, br), 3241 (s, br), 3132 (s), 3107 (s, sh), 2983 (s), 2940 (s), 1742 (vs), 1683 (vs, vbr), 1619 (vs, br), 1560 (vs, sh), 1543 (vs, vbr), 1497 (s), 1473 (s), 1396 (s), 1377 (s), 1367 (s), 1211 (vs), 1177 (vs), 1110 (s), 1096 (s, sh), 983 (m), 973 (m, sh). δ_H (500.0 MHz, DMSO-d_6) 1.19 (3H, t, J(CH_3,CH_2)=7.1, $CH_3$$CH_2$O-Val), 1.25 (3H, t, J(CH_3,CH_2)=7.0,

CH$_3$CH$_2$O), 1.33 (3H, d, *J*(CH$_3$,CH)=7.2, CH$_3$-Val), 3.96 (2H, q, *J*(CH$_2$,CH$_3$)=7.0, OC*H*$_2$CH$_3$), 4.11 (2H, m, CH$_3$C*H*$_2$O-Val), 4.30 (1H, p, *J*(CH,CH$_3$)=*J*(CH,1)=7.2, CH-Val), 5.51 (1H, d, *J*(5,6)=12.3, H-5), 7.59 (1H, d, *J*(6,5)=12.3, H-6), 8.87 (1H, br d, *J*(1,CH)=7.1, H-1), 10.17 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 14.23 (*CH*$_3$CH$_2$O-Val), 14.62 (*CH*$_3$CH$_2$O), 18.04 (CH$_3$-Val), 48.25 (CH-Val), 60.99 (CH$_3$*CH*$_2$O-Val), 67.59 (O*CH*$_2$CH$_3$), 98.40 (C-5), 153.51 (C-2), 162.57 (C-6), 168.05 (C-4), 172.55 (COO-Val). HRMS for $C_{11}H_{18}N_2O_5Na$ $(M+Na)^+$ calcd 281.1108, found 281.1108.

*4.6.20. 1-(1-N-Boc-3-pyrrolidinyl)-3-(3-ethoxy-2-methylacryloyl)-urea (**9m**).* The title compound was prepared according to general method A from compound **8a** (0.45 g, 2.42 mmol) and reagent **7b** in 96% yield (0.79 g, 2.314 mmol) of white solid. ν_{max}(CHCl$_3$) 3439 (w), 3270 (m, br), 2983 (m), 1689 (vs, br), 1655 (s, sh), 1614 (s), 1545 (s), 1487 (m, sh), 1476 (s), 1459 (s), 1412 (s), 1392 (s, sh), 1368 (s), 1165 (s), 1137 (s), 1122 (s), 462 (w). δ_H (500.0 MHz, CDCl$_3$, mixture of two amidic isomers 1:1) 1.36 (6H, t, *J*(CH$_3$,CH$_2$)=7.1, OCH$_2$*CH*$_3$), 1.46 (18H, s, (CH$_3$)$_3$C), 1.78 (6H, d, *J*(CH$_3$,6)=1.2, 5-CH$_3$), 1.89 (2H, br m, H-4′b), 2.16 (2H, dtd, J_{gem}=12.8, *J*(4′a,3′)=7.4, *J*(4′a,5′)=7.4, 6.0, H-4′a), 3.21 and 3.30 (2×1H, 2×bdd, J_{gem}=11.0, *J*(2′b,3′)=4.9, H-2′b), 3.39–3.53 (4H, br m, H-5′), 3.65 (2H, dd, J_{gem}=11.0, *J*(2′a,3′)=6.4, H-2′a), 4.09 (4H, q, *J*(CH$_2$,CH$_3$)=7.1, OC*H*$_2$CH$_3$), 4.39 (2H, br m, H-3′), 7.43 (2H, q, *J*(6,CH$_3$)=1.2, H-6), 8.17 and 8.21 (2×1H, 2×br s, H-3), 8.93 (2H, br d, *J*(1,3′)=6.1, H-1). δ_C (125.7 MHz, CDCl$_3$, mixture of two amidic isomers 1:1) 8.82 (5-CH$_3$), 15.35 (OCH$_2$*CH*$_3$), 28.44 ((**C**H$_3$)$_3$C), 31.07 and 31.89 (C-4′), 43.71 and 44.08 (C-5′), 48.99 and 49.74 (C-3′), 51.27 and 51.62 (C-2′), 70.31 (O*CH*$_2$CH$_3$), 79.46 (**C**(CH$_3$)$_3$), 106.54 and 106.64 (C-5), 153.96 and 154.39 (C-2 and CO), 157.50 and 157.59 (CH-6), 169.53 (C-4). HRMS for $C_{16}H_{27}N_3O_5Na$ $(M+Na)^+$ calcd 364.1843, found 364.1842.

*4.6.21. 1-((3S,4R)-1-N-Boc-3-dimethoxytrityloxy-4-pyrrolidinyl)-3-(3-ethoxy-2-methylacryloyl)urea (**9n**).* The title compound was prepared according to general method A from compound **8b** (0.4 g, 0.79 mmol) and reagent **7b** in 99% yield (0.52 g, 0.79 mmol) of yellowish foam. ν_{max}(KBr) 3360 (w, br, sh), 3255 (m, br), 3130 (w, br), 2976 (m), 2836 (m), 1699 (vs), 1680 (vs, sh), 1663 (s), 1609 (s), 1578 (m), 1538 (s, br), 1510 (vs), 1495 (s, sh), 1476 (s), 1465 (s), 1458 (m, sh), 1446 (m), 1404 (s), 1392 (s, sh), 1366 (m), 1252 (s), 1211 (s), 1176 (s), 1130 (s), 1091 (s), 1034 (s), 1002 (m), 911 (w), 768 (m), 698 (m). δ_H (500.0 MHz, CDCl$_3$, mixture of two amidic isomers 1:1) 1.35 (6H, t, *J*(CH$_3$,CH$_2$)=7.1, OCH$_2$*CH*$_3$), 1.36 and 1.38 (2×9H, 2×s, (CH$_3$)$_3$C), 1.80 and 1.82 (2×3H, 2×br s, 5-CH$_3$), 2.76 (1H, dd, J_{gem}=11.8, *J*(2′b,3′)=7.0, H-2′b), 2.89 (1H, dd, J_{gem}=11.8, *J*(2′a,3′)=7.7, H-2′a), 3.18 (1H, dd, J_{gem}=11.3, *J*(2′b,3′)=7.6, H-2′b), 3.25 and 3.28 (2×1H, 2×dd, J_{gem}=11.8, *J*(5′b,4′)=5.2, H-5′b), 3.31 (1H, dd, J_{gem}=11.3, *J*(2′a,3′)=7.2, H-2′a), 3.40 (1H, m, H-4′), 3.49 and 3.52 (2×1H, 2×dd, J_{gem}=11.8, *J*(5′a,4′)=2.8, H-5′a), 3.777 and 3.780 (2×6H, 2×s, CH$_3$O-DMTr), 3.81 (1H, br m, H-4′), 4.09 (4H, q, *J*(CH$_2$,CH$_3$)=7.1, OC*H*$_2$CH$_3$), 4.13 and 4.16 (2×2H, 2×br m, H-3′), 6.82 (8H, m, H-*m*-C$_6$H$_4$-DMTr), 7.21 (2H, m, H-*p*-C$_6$H$_5$-DMTr), 7.28 (4H, br m, H-*m*-C$_6$H$_5$-DMTr), 7.40 (8H, br m, H-*o*-C$_6$H$_4$-DMTr), 7.44 (2H, q, *J*(6,CH$_3$)=1.2, H-6), 7.50 and 7.51 (2×2H, 2×m, H-*o*-C$_6$H$_5$-DMTr), 7.53 and 7.63 (2×1H, 2×br s, H-3), 9.28 (1H, br d, *J*(1,4′)=6.4, H-1), 9.30 (1H, br d, *J*(1,4′)=5.6, H-1). δ_C (125.7 MHz, CDCl$_3$, mixture of two amidic isomers 1:1) 8.94 (5-CH$_3$), 15.39 (OCH$_2$*CH*$_3$), 28.33 and 28.39 ((**C**H$_3$)$_3$C), 48.47 and 48.88 (C-2′), 49.58 and 50.43 (C-5′), 51.29 and 51.78 (C-4′), 55.19 (CH$_3$O-DMTr), 70.33 (O*CH*$_2$CH$_3$), 71.28 and 71.79 (C-3′), 79.26 and 79.38 (**C**(CH$_3$)$_3$), 87.05 and 87.18 (C-DMTr), 106.20 and 106.38 (C-5), 113.25 (C-*m*-C$_6$H$_4$-DMTr), 126.96 and 127.04 (C-*p*-C$_6$H$_5$-DMTr), 127.92 (C-*m*-C$_6$H$_5$-DMTr), 128.06 and 128.13 (C-*o*-C$_6$H$_5$-DMTr), 130.00 and 130.05 (C-*o*-C$_6$H$_4$-DMTr), 136.02, 136.10 and 136.20 (C-*i*-C$_6$H$_4$-DMTr), 144.91 and 145.00 (C-*i*-C$_6$H$_5$-DMTr), 153.83 and 153.94 (C-2), 154.12 and 154.27 (CO), 157.44 and 157.53 (C-6), 158.73 (C-*p*-C$_6$H$_4$-DMTr), 168.59 and 168.87 (C-4). HRMS for $C_{37}H_{45}N_3O_8Na$ $(M+Na)^+$ calcd 682.3099, found 682.3096.

*4.6.22. 1-Cyclohexyl-3-(3-Ethoxy-2-methylacryloyl)urea (**9o**).* The title compound was prepared according to general method A from **8e** (0.128 g, 1.3 mmol) and reagent **7b** in 82% yield (0.27 g, 1.062 mmol) of white solid. ν_{max}(KBr) 3352 (m), 3261 (s), 3141 (m), 3089 (w), 2986 (m), 2934 (s), 2903 (m), 2854 (m), 1678 (vs), 1657 (vs), 1628 (m, sh), 1612 (m, sh), 1547 (vs), 1490 (m), 1476 (s), 1466 (s), 1454 (s), 1388 (m), 1368 (m), 1295 (s), 1218 (vs), 1040 (m), 764 (m). δ_H (499.8 MHz, CDCl$_3$) 1.34 (3H, t, *J*(CH$_3$,CH$_2$)=7.1, OCH$_2$*CH*$_3$), 1.20–1.40 (5H, m, H-2′,3′,4′,5′,6′ax), 1.58 (1H, m, H-4′eq), 1.71 (2H, m, H-3′eq and H-5′eq), 1.78 (3H, d, *J*(CH$_3$,6)=1.2, 5-CH$_3$), 1.92 (2H, m, H-2′eq and H-6′eq), 3.72 (1H, m, H-1′), 4.08 (2H, q, *J*(CH$_2$,CH$_3$)=7.1, OC*H*$_2$CH$_3$), 7.45 (1H, q, *J*(6,CH$_3$)=1.2, H-6), 8.33 (1H, br s, H-3), 8.73 (1H, br d, *J*(1,1′)=7.8, H-1). δ_C (125.7 MHz, CDCl$_3$) 8.85 (5-CH$_3$), 15.38 (OCH$_2$*CH*$_3$), 24.54 (C-3′ and C-5′), 25.51 (C-4′), 32.88 (C-2′ and C-6′), 48.40 (C-1′), 70.09 (O*CH*$_2$CH$_3$), 107.04 (C-5), 153.52 (C-2), 157.05 (C-6), 169.64 (C-4). HRMS $C_{13}H_{23}N_2O_3$ $(M+H)^+$ calcd 255.1703, found 255.1704.

*4.6.23. 1-(3-Ethoxy-2-methylacryloyl)-3-(trans-2-hydroxycyclohexyl)-urea (**9p**).* The title compound was prepared according to general method D from compound **8f** (0.128 g, 1.3 mmol) and reagent **7b** in 96% yield (0.26 g, 0.962 mmol) of white solid. ν_{max}(KBr) 3432 (s), 3264 (s), 3161 (m), 2983 (w), 2940 (m), 2929 (m), 2904 (m), 2861 (m), 1695 (vs), 1687 (vs, sh), 1666 (s), 1607 (m), 1590 (m), 1543 (s), 1532 (s, sh), 1477 (s), 1467 (m, sh), 1451 (m), 1396 (w), 1388 (w, sh), 1370 (w), 1302 (w, sh), 1292 (w), 1215 (s), 1039 (m), 766 (m). δ_H (499.8 MHz, DMSO-d_6) 1.08–1.26 (4H, m, H-3′ax, 4′ax, 5′ax and H-6′ax), 1.25 (3H, t, *J*(CH$_3$,CH$_2$)=7.1, CH$_2$*CH*$_3$), 1.53 (1H, m, H-5′eq), 1.61 (1H, m, H-4′eq), 1.62 (3H, d, *J*(CH$_3$,6)=1.2, 5-CH$_3$), 1.80 (1H, m, H-6′eq), 1.96 (1H, m, H-3′eq), 3.24 (1H, m, H-1′), 3.38 (1H, m, H-2′), 4.05 (2H, q, *J*(CH$_2$,CH$_3$)=7.1, OC*H*$_2$CH$_3$), 4.75 (1H, d, *J*(OH,1′)=5.4, OH), 7.53 (1H, q, *J*(6,CH$_3$)=1.2, H-6), 8.69 (1H, br d, *J*(1,2′)=7.3, H-1), 9.64 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 9.12 (5-CH$_3$), 15.46 (CH$_2$*CH*$_3$), 23.59 (C-5′), 24.01 (C-4′), 31.00 (C-3′), 34.08 (C-6′), 54.63 (C-2′), 69.49 (O*CH*$_2$CH$_3$), 71.24 (C-1′), 107.10 (C-5), 153.88 (C-2), 156.71 (C-6), 169.83 (C-4). HRMS $C_{13}H_{22}N_2O_4Na$ $(M+Na)^+$ calcd 293.1472, found 293.1473.

*4.6.24. 1-(3-Ethoxy-2-methylacryloyl)-3-(1-hydroxymethylcyclopentyl)urea (**9q**).* The title compound was prepared according to general method B from compound **8h** (0.115 g, 1.0 mmol) and reagent **7b** in 89% yield (0.24 g, 0.888 mmol) of white solid. ν_{max}(KBr) 3282 (s, sh), 3255 (s), 3210 (s, br, sh), 3112 (m), 3085 (m, sh), 2959 (s), 2930 (m), 2870 (m), 1685 (vs), 1655 (vs), 1612 (m, sh), 1556 (vs), 1492 (m), 1477 (m), 1461 (m), 1452 (m), 1389 (m), 1367 (m), 1312 (m, sh),1300 (s), 1226 (s), 1208 (s), 1051 (m), 1034 (m), 767 (m). δ_H (500.0 MHz, CDCl$_3$) 1.33 (3H, t, *J*(CH$_3$,CH$_2$)=7.1, CH$_2$*CH*$_3$), 1.68 (2H, m, H-3′a and H-4′a), 1.77 (2H, m, H-3′b and H-4′b) 1.79 (3H, d, *J*(CH$_3$,6)=1.2, 5-CH$_3$), 1.83–1.87 (4H, m, H-2′ and H-5′), 3.71 (2H, br s, *CH*$_2$OH), 4.09 (2H, q, *J*(CH$_2$,CH$_3$)=7.1, OC*H*$_2$CH$_3$), 4.28 (1H, br s, OH), 7.40 (1H, q, *J*(6,CH$_3$)=1.2, H-6), 8.10 (1H, br s, H-1), 9.11 (1H, br s, H-3). δ_C (125.7 MHz, CDCl$_3$) 8.80 (5-CH$_3$), 15.31 (CH$_2$*CH*$_3$), 23.74 (C-3′ and C-4′), 35.69 (C-2′ and C-5′), 66.27 (C-1′), 69.13 (CH$_2$OH), 70.34 (O*CH*$_2$CH$_3$), 106.57 (C-5), 154.80 (C-2), 157.58 (C-6), 169.70 (C-4). HRMS $C_{13}H_{22}N_2O_4Na$ $(M+Na)^+$ calcd 293.1472, found 293.1472.

*4.6.25. 1-(2,3-Dihydroxypropyl)-3-(3-ethoxy-2-methylacryloyl)urea (**9r**).* A) The title compound was prepared according to general method B from compound **8i** (0.118 g, 1.3 mmol) and reagent **7b** in 63% yield (0.20 g, 0.813 mmol) of white solid. B) The title compound was prepared according to general method A from compound **8i** (0.177 g, 1.95 mmol) and reagent **7d** in 76% yield (0.38 g, 1.54 mmol). ν_{max}(KBr) 3405 (m, vbr), 3259 (m, br), 3160 (m, br, sh), 2986 (w), 2937 (w), 2893 (w), 1700 (s, sh), 1687 (vs), 1663 (s), 1638

(m), 1623 (m, sh), 1591 (m), 1559 (s), 1542 (m, sh), 1506 (w), 1477 (m), 1388 (w, sh), 1368 (w), 1300 (m), 1235 (m, sh), 1212 (s), 1102 (m), 1066 (m), 1035 (m), 761 (m). δ_H (499.8 MHz, DMSO-d_6) 1.25 (3H, t, J(CH_3,CH_2)=7.1, CH_2CH_3), 1.63 (3H, d, J(CH_3,6)=1.2, 5-CH_3), 3.04 (1H, ddd, J_{gem}=13.3, J(1′a,2′)=7.1, J(1′a,1)=4.9, H-1′a), 3.25 (1H, dt, J_{gem}=10.9, J(3′a,OH)=J(3′a,2′)=6.2, H-3′a), 3.31–3.40 (2H, m, H-1′b and H-3′b), 3.51 (1H, m, H-2′), 4.05 (2H, q, J(CH_2,CH_3)=7.1, OCH_2CH_3), 4.61 (1H, t, J(OH,3′)=5.7, 3′-OH), 4.87 (1H, d, J(OH,2′)=5.1, 2′-OH), 7.53 (1H, q, J(6,CH_3)=1.2, H-6), 8.75 (1H, bdd, J(1,1′b)=6.0, J(1,1′a)=5.2, H-1), 9.67 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 9.16 (5-CH_3), 15.49 (CH_2CH_3), 42.56 (C-1′), 63.88 (C-3′), 69.53 (OCH_2CH_3), 70.27 (C-2′), 107.11 (C-5), 154.29 (C-2), 156.77 (C-6), 169.69 (C-4). HRMS for $C_{10}H_{18}N_2O_5Na$ (M+Na)$^+$ calcd 269.1108, found 269.1107.

*4.6.26. 1-(3-Ethoxy-2-methylacryloyl)-3-phenylurea (**9s**).* The title compound was prepared according to general method A from compound **8j** (0.118 g, 1.3 mmol) and reagent **7b** in 87% yield (0.28 g, 1.129 mmol) of white solid. ν_{max}(KBr) 3284 (m), 3197 (w), 3142 (w), 3088 (w), 3059 (w), 2986 (w), 2937 (w), 2887 (w), 1702 (vs), 1676 (s), 1617 (m), 1605 (s, sh), 1592 (vs), 1557 (s), 1541 (s, sh), 1501 (m), 1488 (m, sh), 1475 (m), 1455 (s), 1396 (m), 1388 (m, sh), 1312 (w), 1226 (s, sh), 1210 (vs), 1179 (w), 1155 (w, sh), 1037 (m), 1002 (w, sh), 916 (m), 848 (vw), 757 (s), 690 (m), 618 (vw), 513 (w). δ_H (499.8 MHz, $CDCl_3$) 1.29 (3H, t, J(CH_3,CH_2)=7.1, CH_2CH_3), 1.84 (3H, d, J(CH_3,6)=1.2, 5-CH_3), 4.02 (2H, q, J(CH_2,CH_3)=7.1, OCH_2CH_3), 7.10 (1H, m, H-4′), 7.32 (2H, m, H-3′), 7.50 (1H, q, J(6,CH_3)=1.2, H-6), 7.52 (2H, m, H-2′), 8.53 (1H, br s, H-3), 10.97 (1H, br s, H-1). δ_C (125.7 MHz, $CDCl_3$) 8.87 (5-CH_3), 15.33 (CH_2CH_3), 70.37 (OCH_2CH_3), 106.78 (C-5), 120.55 (C-2′), 124.13 (C-4′), 128.91 (C-3′), 137.40 (C-1′), 152.00 (C-2), 157.83 (C-6), 169.87 (C-4). HRMS for $C_{13}H_{16}N_2O_3Na$ (M+Na)$^+$ calcd 271.1053, found 271.1055.

*4.6.27. 1-(3-Ethoxy-2-methylacryloyl)-3-naphthalen-2-ylurea (**9t**).* The title compound was prepared according to general method A from compound **8m** (0.186 g, 1.3 mmol) and reagent **7b** in 90% yield (0.35 g, 1.174 mmol) of white solid. ν_{max}(KBr) 3268 (m), 3171 (w), 3150 (w), 3054 (w), 2986 (w), 2939 (w), 2898 (w), 1702 (vs), 1668 (s), 1655 (m, sh), 1617 (m), 1605 (m), 1588 (s), 1572 (s), 1512 (w), 1493 (w, sh), 1471 (m), 1396 (w), 1388 (w, sh), 1361 (w), 1286 (w), 1260 (w), 1216 (vs), 1180 (m), 1123 (s), 1042 (w), 1013 (w), 882 (w), 848 (w), 806 (w), 753 (w), 739 (w), 616 (vw), 469 (w). δ_H (499.8 MHz, $CDCl_3$) 1.26 (3H, t, J(CH_3,CH_2)=7.1, CH_2CH_3), 1.87 (3H, d, J(CH_3,6)=1.2, 5-CH_3), 4.02 (2H, q, J(CH_2,CH_3)=7.1, OCH_2CH_3), 7.40 (1H, m, H-6′), 7.46 (1H, m, H-7′), 7.52 (1H, dd, J(3′,4′)=8.7, J(3′,1′)=2.2, H-3′), 7.52 (1H, q, J(6,CH_3)=1.2, H-6), 7.77–7.81 (3H, m, H-4′, H-5′ and H-8′), 8.15 (1H, d, J(1′,3′)=2.1, H-1′), 8.37 (1H, br s, H-3), 11.14 (1H, br s, H-1). δ_C (125.7 MHz, $CDCl_3$) 8.90 (5-CH_3), 15.28 (CH_2CH_3), 70.45 (OCH_2CH_3), 106.57 (C-5), 117.08 (C-1′), 120.58 (C-3′), 124.92 (C-6′), 126.43 (C-7′), 127.54 and 127.58 (C-5′ and C-8′), 128.69 (C-4′), 130.60 (C-4′a), 133.86 (C-8′a), 134.89 (C-2′), 151.92 (C-2), 158.03 (C-6), 169.80 (C-4). HRMS for $C_{17}H_{18}N_2O_3Na$ (M+Na)$^+$ calcd 321.1210, found 321.1209.

*4.6.28. (R)-1-(Pyrrolidin-3-yl)uracil (**10a**).* The title compound was prepared from **9a** (1.72 g, 5.254 mmol) according to general method E in 97% yield (0.92 g, 5.08 mmol) of white solid. NMR and HRMS spectra were identical to those in Ref. 3.

*4.6.29. 1-((3R,4S)-4-Hydroxypyrrolidin-3-yl)uracil (**10b**).* The title compound was prepared from **9b** (1.13 g, 1.75 mmol) according to general method E and was re-purified using preparative reversed-phase HPLC in 90% yield (0.31 g, 1.575 mmol) of white solid. ν_{max}(KBr) 3397 (m), 3312 (m), 2599 (w, vbr), 1698 (vs), 1677 (s), 1620 (w, sh), 1467 (w), 1388 (m), 1270 (m), 1084 (w), 1053 (w), 802 (m), 768 (w). δ_H (600.1 MHz, D_2O) 3.00 (1H, dd, J_{gem}=12.9, J(5′b,4′)=2.8, H-5′b), 3.24 (1H, dd, J_{gem}=12.2, J(2′b,3′)=8.6, H-2′b), 3.35 (1H, dd, J_{gem}=12.9, J(5′a,4′)=5.4, H-5′a), 3.36 (1H, dd, J_{gem}=12.2, J(2′a,3′)=8.4, H-2′a), 4.48 (1H, ddd, J(4′,3′)=5.7, J(4′,5′)=5.4, 2.8, H-4′), 4.90 (1H, ddd, J(3′,2′)=8.6, 8.4, J(3′,4′)=5.7, H-3′), 5.82 (1H, d, J(5,6)=8.0, H-5), 7.68 (1H, d, J(6,5)=8.0, H-6). δ_C (150.9 MHz, D_2O) 48.60 (C-2′), 55.19 (C-5′), 61.16 (C-3′), 72.05 (C-4′), 103.60 (C-5), 147.94 (C-6), 156.38 (C-2), 170.46 (C-4). HRMS for $C_8H_{12}N_3O_3$ (M+H)$^+$ calcd 198.0873, found 198.0873.

*4.6.30. 1-((3S,4S)-4-Hydroxypyrrolidin-3-yl)uracil (**10c**).* The title compound was prepared from **9c** (0.4 g, 0.635 mmol) according to general method E in 80% yield (0.1 g, 0.51 mmol) of white solid. ν_{max}(KBr) 3406 (m, br), 3185 (m, vbr), 1687 (vs, br), 1628 (m, sh), 1459 (m), 1420 (m), 1382 (m), 1270 (m), 1078 (w, br), 810 (w), 764 (w). δ_H (500.0 MHz, D_2O) 2.94 (1H, dd, J_{gem}=12.3, J(5′b,4′)=5.2, H-5′b), 3.16 (1H, dd, J_{gem}=12.7, J(2′b,3′)=5.9, H-2′b), 3.38 (1H, dd, J_{gem}=12.3, J(5′a,4′)=5.9, H-5′a), 3.51 (1H, dd, J_{gem}=12.7, J(2′a,3′)=8.1, H-2′a), 4.59 (1H, ddd, J(4′,5′)=5.9, 5.2, J(4′,3′)=2.7, H-4′), 4.61 (1H, ddd, J(3′,2′)=8.1, 5.9, J(3′,4′)=2.7, H-3′), 5.83 (1H, d, J(5,6)=7.9, H-5), 7.59 (1H, d, J(6,5)=7.9, H-6). δ_C (125.7 MHz, D_2O) 50.55 (C-2′), 54.68 (C-5′), 69.47 (C-3′), 77.63 (C-4′), 104.74 (C-5), 147.76 (C-6), 156.16 (C-2), 170.98 (C-4). HRMS for $C_8H_{12}N_3O_3$ (M+H)$^+$ calcd 198.0873, found 198.0868.

*4.6.31. 1-Cyclopropyluracil (**10d**).* The title compound was prepared from **9d** (0.45 g, 1.988 mmol) according to general method E in 97% yield (0.35 g, 1.944 mmol) of white solid. ν_{max}(KBr) 3145 (w, br), 2998 (m, br), 2954 (m), 2876 (m), 1714 (s, sh), 1700 (vs), 1678 (vs), 1615 (m), 1472 (m), 1453 (w, sh), 1430 (w), 1421 (m), 1384 (m), 1268 (s), 765 (w). δ_H (500.0 MHz, DMSO-d_6) 1.52–1.65 (4H, m, H-2′a, 3′a, 4′a and H-5′a), 1.75 (2H, m, H-3′b and H-4′b), 1.91 (2H, m, H-2′b and H-5′b), 4.70 (1H, m, H-1′), 5.56 (1H, dd, J(5,6)=8.0, J(5,3)=2.3, H-5), 7.65 (1H, d, J(6,5)=8.0, H-6), 11.22 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 23.84 (C-3′ and C-4′), 30.72 (C-2′and C-5′), 56.50 (C-1′), 101.59 (C-5), 142.74 (C-6), 151.32 (C-2), 163.51 (C-4). HRMS $C_9H_{13}N_2O_2$ (M+H)$^+$ calcd 181.0972, found 181.0972.

*4.6.32. 1-Cyclohexyluracil (**10e**).* The title compound was prepared from **9e** (0.50 g, 2.08 mmol) according to general method E in 99% yield (0.40 g, 2.061 mmol) of white solid. ν_{max}(KBr) 2930 (s), 2865 (m), 1714 (vs, sh), 1690 (vs, br), 1676 (vs, br), 1616 (s), 1470 (s), 1452 (m), 1428 (m), 1419 (s), 1379 (s), 1268 (s), 763 (m). δ_H (500.0 MHz, DMSO-d_6) 1.13 (1H, qt, J_{gem}=J(4′ax,3′ax)=J(4′ax,5′ax)=13.0, J(4′ax,3′eq)=J(4′ax,5′eq)=3.6, H-4′ax), 1.32 (2H, qt, J_{gem}=J(3′ax,2′ax)=J(3′ax,4′ax)=13.2, J(3′ax,2′eq)=J(3′ax,4′eq)=3.4, H-3′ax and H-5′ax), 1.54 (2H, qd, J_{gem}=J(2′ax,1′)=J(2′ax,3′ax)=12.4, J(2′ax,3′eq)=3.7, H-2′ax and H-6′ax), 1.61 (1H, dm, J_{gem}=12.9, H-4′eq), 1.69 (2H, m, H-2′eq and H-6′eq), 1.78 (2H, dm, J_{gem}=13.5, H-3′eq and H-5′eq), 4.23 (1H, tt, J(1′,2′ax)=J(1′,6′ax)=12.2, J(1′,2′eq)=J(1′,6′eq)=3.8, H-1′), 5.55 (1H, dd, J(5,6)=8.0, J(5,3)=2.3, H-5), 7.70 (1H, d, J(6,5)=8.0, H-6), 11.22 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 24.85 (C-4′), 25.56 (C-3′ and C-5′), 31.06 (C-2′and C-6′), 54.25 (C-1′), 101.33 (C-5), 142.40 (C-6), 151.10 (C-2), 163.43 (C-4). HRMS $C_{10}H_{14}N_2O_2Na$ (M+Na)$^+$ calcd 217.0947, found 217.0948.

*4.6.33. 1-(trans-2-Hydroxycyclohexyl)uracil (**10f**).* The title compound was prepared from **9f** (0.33 g, 1.28 mmol) according to general method E in 78% yield (0.210 g, 0.998 mmol) of white solid. ν_{max}(KBr) 3348 (s), 3287 (m, br, sh), 3162 (m, br), 3021 (m, br), 2937 (s), 2862 (m), 1728 (s), 1694 (vs, br), 1662 (s, sh), 1625 (s), 1474 (s), 1427 (m), 1457 (m), 1388 (s), 1271 (s), 1074 (m), 764 (w). δ_H (499.8 MHz, DMSO-d_6) 1.21–1.29 (3H, m, H-3′a, 4′a and H-5′a), 1.56 (1H, br s, H-6′a), 1.62–1.71 (3H, m, H-4′b, 5′b and H-6′b), 1.94 (1H, m, H-3′b), 3.64 (1H, br s, H-2′), 4.06 (1H, br s, H-1′), 4.89 (1H, br d, J(OH,2′)=5.0, OH), 5.54 (1H, d, J(5,6)=7.9, H-5), 7.67 (1H, d, J(6,5)=7.9, H-6), 11.12 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6)

24.02 (C-4′), 25.02 (C-5′), 30.08 (C-6′), 35.14 (C-3′), 60.36 (C-1′), 69.00 (C-2′), 100.98 (C-5), 142.86 (C-6), 151.61 (C-2), 163.46 (C-4). HRMS for $C_{10}H_{15}N_2O_3$ $(M+H)^+$ calcd 211.1077, found 211.1078.

*4.6.34. 1-(cis-2-Hydroxycyclopentyl)uracil (**10g**).* The title compound was prepared from **9g** (0.28 g, 1.155 mmol) according to general method E in 95% yield (0.215 g, 0.153 mmol) of white solid. ν_{max}(KBr) 3470 (m), 3418 (m, br), 3288 (w, br, sh), 3165 (m), 3024 (m, br), 2964 (m), 2873 (w), 1701 (vs), 1691 (vs), 1665 (s, sh), 1619 (m), 1473 (m), 1453 (w, sh), 1425 (w), 1393 (w), 1277 (m), 1015 (w), 762 (w). δ_H (499.8 MHz, DMSO-d_6) 1.48–1.61 (2H, m, H-3′a and H-4′a), 1.75–1.83 (2H, m, H-4′b and H-5′a), 1.85–1.95 (2H, m, H-3′b and H-5′b), 4.03 (1H, m, H-2′), 4.50 (1H, m, H-1′), 4.93 (1H, br d, J(OH,2′)=4.2, OH), 5.48 (1H, dd, J(5,6)=8.0, J(5,3)=2.3, H-5), 7.60 (1H, d, J(6,5)=8.1, H-6), 11.16 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 20.05 (C-4′), 26.05 (C-5′), 32.79 (C-3′), 58.56 (C-1′), 69.62 (C-2′), 99.63 (C-5), 144.22 (C-6), 151.71 (C-2), 163.56 (C-4). HRMS for $C_9H_{12}N_2O_3Na$ $(M+Na)^+$ calcd 219.0740, found 219.0741.

*4.6.35. 1-(1-(Hydroxymethyl)cyclopentyl)uracil (**10h**).* The title compound was prepared from **9h** (0.53 g, 2.067 mmol) according to general method E in 92% yield (0.402 g, 1.914 mmol) of white solid. ν_{max}(KBr) 3404 (s), 3176 (m), 3054 (m, br), 2956 (m), 2879 (m), 1705 (vs), 1689 (vs), 1662 (vs), 1617 (w), 1465 (m), 1415 (m), 1387 (m), 1265 (w), 1062 (m), 764 (m). δ_H (500.0 MHz, DMSO-d_6) 1.55 (2H, m, H-3′a and H-4′a), 1.65 (2H, m, H-3′b and H-4′b), 1.78 (2H, m, H-2′a and H-5′a), 2.15 (2H, m, H-2′b and H-5′b), 3.49 (2H, s, CH_2O), 5.06 (1H, br s, OH), 5.41 (1H, dd, J(5,6)=8.1, J(5,3)=2.5, H-5), 7.47 (1H, d, J(6,5)=8.2, H-6), 11.01 (1H, br d, J(3,5)=2.2, H-3). δ_C (125.7 MHz, DMSO-d_6) 22.35 (C-3′ and C-4′), 33.78 (C-2′and C-5′), 61.59 (CH_2OH), 73.42 (C-1′), 99.49 (C-5), 145.75 (C-6), 151.37 (C-2), 164.00 (C-4). HRMS $C_{10}H_{14}N_2O_3Na$ $(M+Na)^+$ calcd 233.0897, found 233.0896.

*4.6.36. 1-(2,3-Dihydroxypropyl)uracil (**10i**).* The title compound was prepared from **9i** (0.37 g, 1.59 mmol) according to general method E in 97% yield (0.29 g, 1.559 mmol) of white solid. ν_{max}(KBr) 3424 (br), 3375 (s, br), 3150 (m, br, sh), 3101 (m), 1689 (vs, sh), 1663 (vs, br), 1620 (s), 1469 (m), 1429 (s), 1391 (m), 1250 (m), 1085 or 1068 (m), 1047 (m), 764 (m). δ_H (500.0 MHz, DMSO-d_6) 3.29 (1H, dd, J_{gem}=11.1, J(3′a,2′)=5.9, H-3′a), 3.36 (1H, dd, J_{gem}=11.1, J(3′b,2′)=5.2, H-3′b), 3.36 (1H, dd, J_{gem}=13.7, J(1′a,2′)=8.8, H-1′a), 3.67 (1H, m, H-2′), 3.92 (1H, dd, J_{gem}=13.7, J(1′b,2′)=3.5, H-1′b), 5.50 (1H, dd, J(5,6)=7.8, J(5,3)=2.3, H-5), 7.49 (1H, d, J(6,5)=7.9, H-6), 11.22 (1H, br d, J(3,5)=2.1, H-3). δ_C (125.7 MHz, DMSO-d_6) 51.38 (C-1′), 63.92 (C-3′), 69.30 (C-2′), 100.28 (C-5), 147.36 (C-6), 151.40 (C-2), 164.25 (C-4). HRMS $C_7H_{10}N_2O_4Na$ $(M+Na)^+$ calcd 209.0533, found 209.0534.

*4.6.37. 1-Phenyluracil (**10j**).* The title compound was prepared from **9j** (0.4 g, 0.635 mmol) according to general method E in 96% yield (0.17 g, 0.903 mmol) of white solid. ν_{max}(KBr) 3159 (w, br), 1779 (m), 1745 (s), 1716 (m), 1692 (vs), 1663 (m, sh), 1628 (m), 1601 (m), 1579 (w, sh), 1494 (w), 1460 (w), 1440 (m), 1423 (m), 1384 (s), 1321 (vw), 1258 (m), 1182 (vw), 1075 (w), 1034 (w), 999 (w), 909 (w), 824 (m), 757 (m), 688 (m), 507 (w). δ_H (500.0 MHz, $CDCl_3$) 5.83 (1H, dd, J(5,6)=8.0, J(5,3)=2.2, H-5), 7.34 (1H, d, J(6,5)=8.0, H-6), 7.35 (2H, m, H-*o*-Ph), 7.45 (1H, m, H-*p*-Ph), 7.50 (2H, m, H-*m*-Ph), 8.39 (1H, br s, H-3). δ_C (125.7 MHz, $CDCl_3$) 102.65 (C-5), 126.26 (C-*o*-Ph), 129.05 (C-*p*-Ph), 129.70 (C-*m*-Ph), 138.32 (C-*i*-Ph), 144.64 (C-6), 149.96 (C-2), 162.95 (C-4). HRMS for $C_{10}H_9N_2O_2$ $(M+H)^+$ calcd 189.0659, found 189.0658.

*4.6.38. Methyl 2-(1-uracilyl)acetate (**10k**).* The title compound was prepared from **9k** (0.74 g, 3.21 mmol) according to general method E in 78% yield (0.46 g, 2.5 mmol) of white solid. ν_{max}(KBr) 3183 (m, br), 1739 (vs), 1700 (vs, br), 1634 (s), 1454 (s), 1440 (m, sh), 1419 (m), 1381 (m), 1250 (s, sh), 1235 (s), 1223 (s), 822 (m), 768 (m), 760 (m). δ_H (500.0 MHz, DMSO-d_6) 3.68 (3H, s, CH_3O), 4.52 (2H, s, CH_2N), 5.62 (1H, dd, J(5,6)=7.9, J(5,3)=2.2, H-5), 7.61 (1H, d, J(6,5)=7.9, H-6), 11.42 (1H, br d, J(3,5)=2.2, H-3). δ_C (125.7 MHz, DMSO-d_6) 48.33 (CH_2N), 52.62 (CH_3O), 101.42 (C-5), 146.18 (C-6), 151.25 (C-2), 164.09 (C-4), 168.97 (CO). HRMS for $C_7H_8N_2O_4Na$ $(M+H+Na)^+$ calcd 207.0376, found 207.0377.

*4.6.39. (R)-Ethyl 2-(1-uracilyl)propanoate (**10l**).* The title compound was prepared from **9l** (0.73 g, 2.83 mmol) according to general method E in 96% yield (0.58 g, 2.73 mmol) of white solid. ν_{max}(KBr) 3150 (m, br), 1754 (s), 1746 (vs), 1713 (vs), 1672 (vs), 1617 (s, sh), 1480 (m), 1471 (m), 1459 (m), 1415 (m), 1399 (m), 1380 (s), 1272 (s), 1203 (s, sh), 1191 (s), 1115 (w), 1097 (w, sh), 830 (m), 822 (m), 679 (w), 760 (w). δ_H (500.0 MHz, DMSO-d_6) 1.17 (3H, t, J(CH_3,CH_2)=7.1, CH_3CH_2O), 1.52 (3H, d, J(CH_3,CH)=7.3, CH_3), 4.13 (2H, m, CH_3CH_2O), 4.98 (1H, q, J(CH,CH_3)=7.3, CH), 5.60 (1H, dd, J(5,6)=8.0, J(5,3)=2.2, H-5), 7.66 (1H, d, J(6,5)=8.0, H-6), 11.32 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 14.16 (CH_3CH_2O), 15.46 (CH_3), 54.94 (CH), 61.46 (CH_3CH_2O), 101.38 (C-5), 144.15 (C-6), 150.92 (C-2), 163.58 (C-4), 170.19 (CO). HRMS for $C_9H_{12}N_2O_4Na$ $(M+H+Na)^+$ calcd 235.0689, found 235.0689.

*4.6.40. (R)-1-(Pyrrolidin-3-yl)thymine (**10m**).* The title compound was prepared from **9m** (0.79 g, 2.314 mmol) according to general method E in 93% yield (0.42 g, 2.15 mmol) of white solid. NMR and HRMS spectra were identical to those in Ref. 3.

*4.6.41. 1-((3R,4S)-4-Hydroxypyrrolidin-3-yl)thymine (**10n**).* The title compound was prepared from **9n** (0.52 g, 0.79 mmol) according to general method E and was re-purified using preparative reverse phase HPLC in 90% yield (0.15 g, 0.71 mmol) of white solid. NMR and HRMS spectra were identical to those in Ref. 4.

*4.6.42. 1-Cyclohexylthymine (**10o**).* The title compound was prepared from **9o** (0.27 g, 1.06 mmol) according to general method E in 95% yield (0.21 g, 1.008 mmol) of white solid. ν_{max}(KBr) 3395 (w), 3167 (s), 3100 (s, br), 3042 (s, br), 2931 (s), 2858 (s), 1692 (vs, br), 1661 (vs, br), 1517 (w), 1473 (s), 1451 (s), 1419 (m), 1392 (s), 1368 (m), 1271 (vs), 1046 (w), 759 (m). δ_H (500.0 MHz, $CDCl_3$) 1.18 (1H, m, H-4′ax), 1.39–1.50 (4H, m, H-2′ax, 3′ax, 5′ax and H-6′ax), 1.74 (1H, dm, J_{gem}=13.2, H-4′eq), 1.86–1.92 (4H, m, H-2′eq, 3′eq, 4′eq and H-6′eq), 1.93 (3H, d, J(CH_3,6)=1.2, CH_3), 4.46 (1H, m, H-1′), 7.06 (1H, q, J(6,CH_3)=1.2, H-6), 9.34 (1H, br s, H-3). δ_C (125.7 MHz, $CDCl_3$) 12.54 (CH_3), 25.12 (C-4′), 25.53 (C-3′ and C-5′), 31.87 (C-2′and C-6′), 54.33 (C-1′), 110.44 (C-5), 136.51 (C-6), 151.03 (C-2), 163.79 (C-4). HRMS $C_{11}H_{17}N_2O_2$ $(M+H)^+$ calcd 209.1285, found 209.1284.

*4.6.43. 1-(trans-2-Hydroxycyclohexyl)thymine (**10p**).* The title compound was prepared from **9p** (0.25 g, 0.924 mmol) according to general method E in 96% yield (0.20 g, 0.892 mmol) of white solid. ν_{max}(KBr) 3459 (s), 3335 (w, br, sh), 3150 (m, br), 3021 (m, br), 2939 (m), 2858 (m), 1696 (vs, sh), 1685 (vs), 1663 (vs), 1514 (w), 1477 (m), 1454 (m), 1428 (m), 1390 (m), 1374 (m), 1271 (s), 1068 (m), 1046 (w, sh), 764 (w), 758 (w). δ_H (499.8 MHz, DMSO-d_6) 1.20–1.31 (3H, m, H-3′a, 4′a and H-5′a), 1.58 (1H, br s, H-6′a), 1.62–1.71 (3H, m, H-4′b, 5′b and H-6′b), 1.77 (3H, br s, CH_3), 1.94 (1H, m, H-3′b), 3.65 (1H, br s, H-2′), 4.06 (1H, br s, H-1′), 4.73 (1H, br s, OH), 7.56 (1H, br s, H-6), 11.07 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 12.29 (CH_3), 24.07 (C-4′), 25.05 (C-5′), 30.09 (C-6′), 35.14 (C-3′), 59.45 (C-1′), 68.97 (C-2′), 108.53 (C-5), 138.47 (C-6), 151.58 (C-2), 164.03 (C-4). HRMS $C_{11}H_{17}N_2O_3$ $(M+H)^+$ calcd 225.1234, found 225.1234.

*4.6.44. 1-(1-(Hydroxymethyl)cyclopentyl)thymine (**10q**).* The title compound was prepared from **9q** (0.30 g, 0.90 mmol) according to general method E in 97% yield (0.195 g, 0.870 mmol) of white solid. ν_{max}(KBr) 3428 (m, sh), 3355 (s), 3150 (m), 3090 (m), 3027 (s), 2954 (s), 2880 (m), 1716 (vs), 1664 (vs), 1478 (m), 1465 (m), 1451 (m),

1424 (m), 1389 (m), 1365 (m), 1268 (m), 1054 (s), 1037 (m), 763 (m), 758 (m). δ_H (499.8 MHz, DMSO-d_6) 1.55 (2H, m, H-3′a and H-4′a), 1.65 (2H, m, H-3′b and H-4′b), 1.75 (3H, d, J(CH_3,6)=1.1, CH_3), 1.80 (2H, m, H-2′a and H-5′a), 2.17 (2H, m, H-2′b and H-5′b), 3.50 (2H, d, J(CH_2,OH)=5.9, CH_2O), 4.97 (1H, t, J(OH,CH_2)=5.9, OH), 7.33 (1H, q, J(6,CH_3)=1.2, H-6), 10.96 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 12.37 (CH_3), 22.34 (C-3′ and C-4′), 33.83 (C-2′and C-5′), 61.60 (CH_2OH), 73.07 (C-1′), 106.71 (C-5), 141.34 (C-6), 151.25 (C-2), 164.42 (C-4). HRMS $C_{11}H_{17}N_2O_3$ $(M+H)^+$ calcd 225.1234, found 225.1234.

*4.6.45. 1-(2,3-Dihydroxypropyl)thymine (**10r**).* The title compound was prepared from **9r** (0.19 g, 0.90 mmol) according to general method E in 97% yield (0.195 g, 0.870 mmol) of white solid. ν_{max}(KBr) 3494 (s), 3392 (s, br), 3280 (m, br, sh), 3145 (m, br), 1700 (s, sh), 1678 (vs), 1642 (s, sh), 1520 (vw), 1482 (m), 1429 (m), 1389 (m), 1096 (s), 1044 (m), 763 (m). δ_H (499.8 MHz, DMSO-d_6) 1.74 (3H, d, J(CH_3,6)=1.2, CH_3), 3.30 (1H, dd, J_{gem}=11.1, J(3′a,2′)=5.8, H-3′a), 3.36 (1H, dd, J_{gem}=11.1, J(3′b,2′)=5.2, H-3′b), 3.36 (1H, dd, J_{gem}=13.7, J(1′a,2′)=8.6, H-1′a), 3.68 (1H, m, H-2′), 3.87 (1H, dd, J_{gem}=13.7, J(1′b,2′)=3.6, H-1′b), 7.38 (1H, q, J(6,CH_3)=1.2, H-6), 11.17 (1H, br s, H-3). δ_C (125.7 MHz, DMSO-d_6) 12.18 (CH_3), 51.11 (C-1′), 63.88 (C-3′), 69.34 (C-2′), 107.66 (C-5), 143.11 (C-6), 151.31 (C-2), 164.65 (C-4). HRMS $C_8H_{11}N_2O_4$ $(M+H)^+$ calcd 199.0713, found 199.0722.

*4.6.46. 1-Phenylthymine (**10s**).* The title compound was prepared from **9s** (0.26 g, 1.04 mmol) according to general method E in 97% yield (0.205 g, 1.014 mmol) of white solid. ν_{max}(KBr) 3166 (s, br), 3101 (m), 3038 (s, br), 1700 (vs, br), 1664 (vs, br), 1650 (vs, br), 1595 (vs), 1508 (m), 1491 (vs), 1478 (s), 1469 (s), 1446 (s), 1432 (s), 1419 (s), 1385 (m), 1371 (s), 1318 (s), 1279 (vs), 1172 (m), 1156 (w), 1080 (w), 1036 (s), 1006 (w), 965 (w), 916 (s), 841 (m), 761 (s), 692 (s), 615 (w), 515 (m). δ_H (499.8 MHz, $CDCl_3$) 1.97 (3H, d, J(CH_3,6)=1.3, CH_3), 7.18 (1H, q, J(6,CH_3)=1.3, H-6), 7.34 (2H, m, H-2′), 7.41 (1H, m, H-4′), 7.48 (2H, m, H-3′), 9.09 (1H, br s, H-3). δ_C (125.7 MHz, $CDCl_3$) 12.23 (CH_3), 111.08 (C-5), 126.28 (C-2′), 128.66 (C-4′), 129.51 (C-3′), 138.57 (C-1′), 140.66 (C-6), 150.26 (C-2), 164.15 (C-4). HRMS for $C_{11}H_{11}N_2O_2$ $(M+H)^+$ calcd 203.0815, found 203.0815.

*4.6.47. 1-(2-Naphthyl)thymine (**10t**).* The title compound was prepared from **9t** (0.33 g, 1.106 mmol) according to general method E in 97% yield (0.27 g, 1.071 mmol) of white solid. ν_{max}(KBr) 3170 (s, br), 3049 (s, br), 1704 (vs, br), 1684 (vs, br), 1655 (vs, sh), 1631 (s), 1598 (s), 1508 (s), 1468 (s), 1455 (s), 1437 (s), 1423 (s), 1373 (s), 1377 (s), 1359 (m), 1293 (vs), 1272 (s), 1142 (w), 1127 (m), 1043 (m), 1019 (w), 955 (w), 946 (w), 887 (m, sh), 866 (s), 810 (s), 772 (m), 765 (s), 753 (s), 649 (m), 629 (w), 527 (w), 477 (s). δ_H (499.8 MHz, $CDCl_3$) 2.04 (3H, d, J(CH_3,6)=1.3, CH_3), 7.29 (1H, q, J(6,CH_3)=1.3, H-6), 7.46 (1H, dd, J(3′,4′)=8.7, J(3′,1′)=2.2, H-3′), 7.54–7.58 (2H, m, H-6′ and H-7′), 7.80 (1H, d, J(1′,3′)=2.3, H-1′), 7.85–7.91 (2H, m, H-5′ and H-8′), 7.95 (1H, d, J(4′,3′)=8.7, H-4′), 8.60 (1H, br s, H-3). δ_C (125.7 MHz, $CDCl_3$) 12.30 (CH_3), 111.20 (C-5), 124.05 (C-3′), 124.87 (C-1′), 127.11 and 127.19 (C-6′ and C-7′), 127.83 and 128.01 (C-5′ and C-8′), 129.59 (C-4′), 132.78 (C-4′a), 133.26 (C-8′a), 136.06 (C-2′), 140.88 (C-6), 150.29 (C-2), 163.92 (C-4). HRMS for $C_{15}H_{13}N_2O_2$ $(M+H)^+$ calcd 253.0972, found 253.0972.

*4.6.48. Methyl 3-ethoxy-2-methylacryloylcarbamate (**11**).* A sample of **7b** was dissolved in 5 ml of anhydrous methanol. Few drops of triethylamine was added. The mixture was evaporated and dissolved in $CDCl_3$. δ_H (500.0 MHz, $CDCl_3$) 1.33 (3H, t, J(CH_3,CH_2)=7.1, CH_3), 1.83 (3H, d, J(CH_3,6)=1.2, 5-CH_3), 3.79 (3H, s, CH_3O), 4.08 (2H, q, J(CH_2,CH_3)=7.1, OCH_2CH_3), 7.42 (1H, q, J(6,CH_3)=1.2, H-6), 7.79 (1H, br s, H-3). δ_C (125.7 MHz, $CDCl_3$) 9.07 (5-CH_3), 15.26 (CH_3), 52.72 (CH_3O), 70.12 (OCH_2CH_3), 107.09 (C-5), 151.93 (C-2), 157.59 (C-6), 165.97 (C-4). HRMS for $C_8H_{13}NO_4Na$ $(M+H+Na)^+$ calcd 210.0742, found 210.0741.

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