Synthesis of *N*-1-Alkylated 6-Benzyluracil-5-carboxylic Esters as Potential Non-Nucleoside Reverse Transcriptase Inhibitors

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Abstract: A series of *N*-1-alkylated 6-benzyluracil-5-carboxylic esters **4a**–**h** were synthesized by reacting imines of 3-oxo-4-phenylbutyrates with *N*-(chlorocarbonyl) isocyanate. An *N*-1-(4-methoxybenzyl) group could be removed in a dealkylation reaction to give the ethyl and allyl esters **5a** and **5b**, respectively. They were *N*-1-alkylated with chloromethyl ethyl ether or dialloxymethane. Unfortunately no biological activity against HIV-1 and HSV was observed for any of the synthesized compounds.

Key words: HIV-1, HSV, non-nucleoside reverse transcriptase inhibitors, uracil-5-carboxylic esters, Emivirine

Non-nucleoside reverse transcriptase inhibitors (NNRTI) of HIV are a very broad class of structurally diverse molecules but they show similarity in their 3-D structures. To date, three compounds from this class have been approved by the FDA and they include Nevirapine,[1–4] Delavirdine[5–7] and Efavirenz.[8,9] Furthermore Emivirine (formerly known as MKC-442, Figure 1) was in Phase III clinical trials and this compound serves as a lead in our NNRTI research program. Recently, a rather new class of NNRTIs, the pyridinones, were synthesized by Dollè et al.[10–12] (Figure 1). Especially 3-carbethoxy-5-ethyl-6-methyl-4-[(3,5-dimethylphenyl)thio]pyridine-2(1*H*)-one has shown high activity against HIV-1 (EC_{50} = 3 nM). Until now, the crystal structures of these inhibitors complexed with reverse transcriptase (RT) remain to be published and therefore no current information is available on the exact binding of these molecules to the enzyme. One can imagine that the orientation of pyridinones when complexed to the RT can be in either of the two orientations shown in Figure 1. The ester group occupies either the C-5 or N-1 position of Emivirine. It was therefore decided to synthesize *N*-1-alkylated 5-ethoxycarbonyl-6-benzyl-uracils because they can be looked at as hybrids of pyridinones and Emivirine with two possible orientations in RT, like the pyridinones as shown in Figure 1.

Analogues of Emivirine have previously been synthesized using 1,3-oxazine-2,4-diones as intermediates.[13,14] The use of this oxazine-strategy gave easy access to pyrimidines by the use of ketones as starting materials[15] and when we tested this strategy on a β-keto ester we obtained

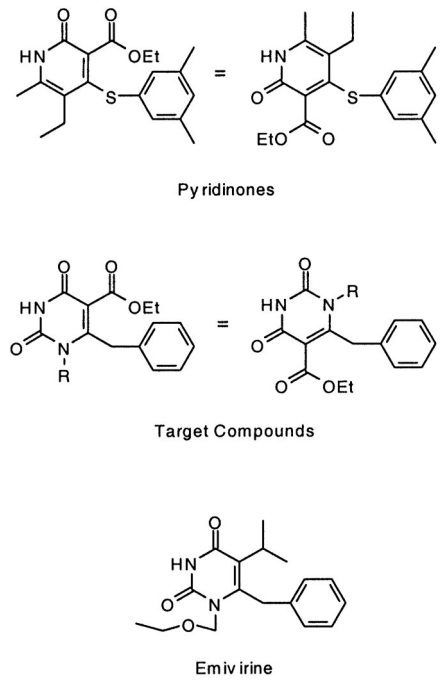
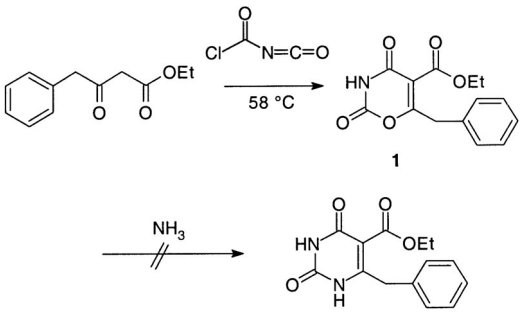


Figure 1

the corresponding 6-benzyl-5-carbethoxy-1,3-oxazine-2,4(3*H*)-dione (**1**) in 50% yield (Scheme 1).

However, it was not possible to obtain the desired pyrimidine by reaction with ammonia in analogy with the above-mentioned method.

Therefore it was decided to introduce the *N*-substituent or a suitable nitrogen protecting group into the molecule before making the ring closure with *N*-(chlorocarbonyl) iso-



Scheme 1

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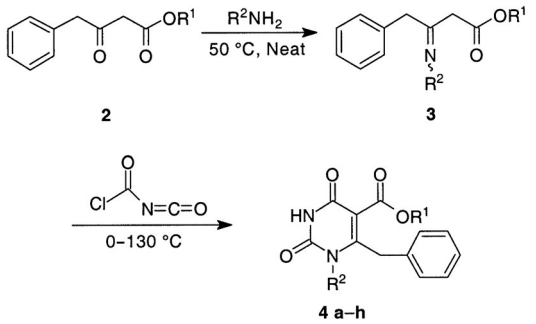
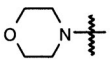
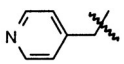
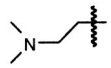
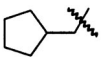
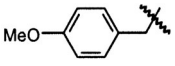
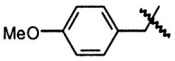
cyanate. The reactions of imines with *N*-(chlorocarbonyl) isocyanate have been reported to give uracils in excellent yields.[16–18] The inspiration came from Grohe and Heitzer who made an analogous reaction with ethyl acetoacetate isolating 5-ethoxycarbonyluracils in 50–76% yield.[19] The advantage of this method is the easily prepared imines from the reaction of primary amines with the β-keto ester to give only one product originating from the major enamine tautomer.



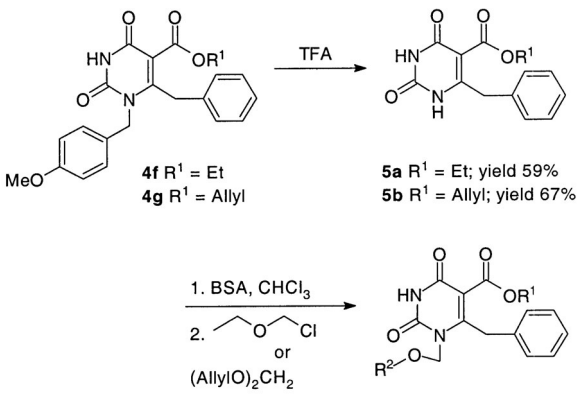
Scheme 2

Table 1 Preparation of Uracils from Imines

4	R^1	R^2	Yield (%)
a	Et		56
b	Et		42
c	Et		65
d	Et		39
e	Et		71
f	Et		59
g	Allyl		57
h	Allyl		62

Ethyl 3-oxo-4-phenylbutyrate or its corresponding allyl 3-oxo-4-phenylbutyrate prepared by transesterification as reported by Mottet et al.[20] were used for the synthesis of the imines **3a**–**h** (Scheme 2). The synthesis was performed by heating a neat 1:1 mixture of the β-keto ester and the amine at 50 °C until TLC showed no more reaction. The corresponding crude enamine/imine was reacted at 0–5 °C in dioxane with *N*-(chlorocarbonyl) isocyanate with subsequent refluxing of the mixture. In this way the uracils **4a**–**h** were synthesized in 39–71% yields. All the amines were commercially available, except for cyclopentylmethyl amine which was synthesized by a modified method of Gribble et al.[21] using sodium for reduction of the corresponding nitrile in 94% yield.

For **4f**,**g** the deprotection of the 4-methoxybenzyl group (PMB) was unsuccessful with usual reagents like CAN,[22–24] DDQ,[25] $TiCl_4$[26] and HCO_2NH_4/10% Pd-C[27,28] which gave no or multiple products. However, deprotection using trifluoroacetic acid[29] afforded the pyrimidines **5a** and **5b** in 59% and 67% yields, respectively. The alkylation to give the target compounds **6a**–**c** in 45–55% yield was done using standard conditions (Scheme 3).



Scheme 3

Table 2 Preparation of Uracils 6 from Uracils 4

6	R^1	R^2	Yield (%)
a	Et	Et	55
b	Allyl	Et	49
c	Et	Allyl	45

All the synthesized compounds were tested for antiviral activity against HIV-1 and HSV, but unfortunately without showing any activity. It was believed that the 5-ester group in **4a**–**h** and **6a**–**c** would be able to induce the 181Tyr switch and thereby have the potential to gain extra hydrogen bonding by forming a hydrogen bond to Glu 138. However, this hypothesis had to be abandoned since no activity was observed. Therefore we have to conclude that pyrimidines having an ester group in the 5-position are not able to bind to the hydrophobic pocket of RT.

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR with TMS as the internal standard. EIMS were recorded on a Finnigan Mat SSQ 701 spectrometer whereas MALDI spectra were recorded on a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Melting points were determined on a Büchi melting point apparatus. Elemental analyses were performed at H.C. Ørsted Institute, University of Copenhagen. Silica gel (0.040–0.063 mm) used for column chromatography and analytical silica gel TLC plates 60 F_{254} were purchased from Merck. Solvents for column chromatography were distilled prior to use. Et_2O, toluene and THF were dried over sodium threads. MeCN was distilled over 1% (w/w) P_2O_5 and then over 5% (w/w) K_2CO_3 and kept over 3 Å molecular sieves. Dioxane was pre-dried over KOH and kept over 3 Å molecular sieves. The

rest of the solvents were used as purchased. The petroleum ether used had a boiling point range of 60–80 °C.

6-Benzyl-5-carbethoxy-1,3-oxazine-2,4(3*H*)-dione (1); Typical Procedure

Ethyl 3-oxo-4-phenylbutyrate (5 g, 24.5 mmol) was mixed with *N*-(chlorocarbonyl) isocyanate (1.97 ml, 24.5 mmol) in a 100 mL 3-necked flask fitted with a septum, a condenser and the mixture was heated at 58 °C for 2 h under a N_2 atmosphere. After further heating at 130 °C for 1 h and then cooling to r.t., the mixture was taken up in EtOAc (100 mL) and the organic phase was washed with sat. $NaHCO_3$ (2 × 50 mL, to remove traces of HCl) followed by washing with H_2O (2 × 50 mL). The organic phase was dried (Na_2SO_4) and evaporated in vacuo to an oily product which was purified by silica gel column chromatography with EtOAc–petroleum ether (1:1) to give compound **1** as a white solid; yield: 3.3 g (50%); mp 120–123 °C.

^{1}H NMR ($CDCl_3$): δ = 1.40 (t, *J* = 7.0 Hz, 3 H, CH_3), 3.95 (s, 2 H, C*H*$_2$Ph), 4.35 (q, *J* = 7.0 Hz, 2 H, CH_2), 7.25–7.35 (m, 5 H, H_{arom}), 9.30 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 13.88 (CH_3), 37.58 (*C*H$_2$Ph), 62.56 (CH_2), 109.19 (C-5), 128.41, 129.67, 129.92, 133.28 (C_{arom}), 146.02 (C-2), 159.33 (C-6), 162.36 (C-4), 169.87 (COO).

EIMS: *m*/*z* = 275 [M^+].

Anal. Calcd for $C_{14}H_{13}NO_5$: 275.26: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.20; H, 4.81; N, 4.99.

Preparation of *N*-1 Substituted Uracil-5-carboxylic Esters 4a-h; General Procedure

To the β-keto ester **2** (4.9 mmol) was added the appropriate primary amine (4.9 mmol) and the mixture was heated to 70–80 °C until TLC showed that no more product was formed. Then the reaction mixture was left on the oil-pump overnight. The resulting solid or oily product was then dissolved in anhyd dioxane (25 mL) and the mixture was cooled in an ice bath under N_2 atmosphere. *N*-(Chlorocarbonyl) isocyanate (5.39 mmol) was added slowly by syringe and a precipitate was formed. In the case where the primary amine contained a basic side chain, Et_3N (4.9 mmol) was added. Then the reaction mixture was refluxed for 2 h and after cooling water (100 mL) was carefully added. The mixture was extracted with EtOAc (2 × 100 mL), dried (Na_2SO_4) and evaporated in vacuo. The product was purified by silica gel column chromatography with EtOAc–petroleum ether (1:1) to give compounds **4a**–**h**.

6-Benzyl-5-ethoxycarbonyl-1-morpholinouracil (4a)

Yield: 0.98 g (56%); white solid; mp 201–202 °C.

^{1}H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.10 (m, 1 H, CH_2, morpholino), 3.20 (m, 1 H, CH_2, morpholino), 3.50–3.95 (m, 6 H, 3 × CH_2, morpholino), 4.01 (s, 2 H, C*H*$_2$Ph), 4.33 (q, *J* = 7.0 Hz, 2 H, OCH_2), 7.23–7.50 (m, 5 H, H_{arom}), 9.56 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 13.97 (CH_3), 36.57 (*C*H$_2$Ph), 51.16 (2 × NCH_2), 62.15 (OCH_2), 66.50 (2 × OCH_2), 110.01 (C-5), 127.11, 127.54, 128.40, 135.63 (C_{arom}), 149.30 (C-2), 157.92 (C-6), 159.72 (C-4), 164.23 (COO).

EIMS: *m*/*z* = 359 [M^+].

Anal. Calcd for $C_{18}H_{21}N_3O_5$: 359.39: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.14; H, 6.12; N, 11.57.

6-Benzyl-5-ethoxycarbonyl-1-(4-pyridylmethyl)uracil (4b)

Yield: 0.75 g (42%); red solid; mp 242–245 °C.

^{1}H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7.0 Hz, 3 H, CH_3), 3.31 (s, 2 H, C*H*$_2$Ph), 4.34 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.95 (s, 2 H, NCH_2), 7.01 (m, 2 H, pyridine-H), 7.20–7.49 (m, 5 H, H_{arom}), 8.30 (m, 2 H, pyridine-H).

^{13}C NMR ($CDCl_3$): δ = 13.91 (CH_3), 36.24 (*C*H$_2$Ph), 46.00 (NCH_2), 62.20 (OCH_2), 112.01 (C-5), 120.61 (C-pyridine), 127.73, 129.44, 133.38 (C_{arom}), 144.93 (C-pyridine), 150.03 (C-pyridine), 151.02 (C-2), 154.11 (C-6), 160.03 (C-4), 164.22 (COO).

EIMS: *m*/*z* = 365 [M^+].

Anal. Calcd for $C_{20}H_{19}N_3O_4$ 365.39: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.81; H, 5.31; N, 11.39.

6-Benzyl-5-ethoxycarbonyl-1-(*N*,*N*-dimethylaminoethyl)uracil (4c)

Yield: 0.65 g (39%); light yellow solid; mp 229–233 °C.

^{1}H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.21 (s, 6 H, 2 × NCH_3), 2.36 (t, *J* = 7.0 Hz, 2 H, NCH_2), 3.78 (t, *J* = 7.0 Hz, 2 H, NCH_2), 4.12 (s, 2 H, C*H*$_2$Ph), 4.26 (q, *J* = 7.0 Hz, 2 H, OCH_2), 7.23–7.34 (m, 5 H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 13.95 (OCH_2CH_3), 36.24 (*C*H$_2$Ph), 42.91 (NCH_2), 45.46 (2 × NCH_3), 57.26 (NCH_2), 61.98 (OCH_2), 111.15 (C-5), 127.52, 128.07, 129.34, 134.27 (C_{arom}), 150.76 (C-2), 154.96 (C-6), 160.20 (C-4), 164.66 (COO).

EIMS: *m*/*z* = 345 [M^+].

Anal. Calcd for $C_{18}H_{23}N_3O_4$ 345.40: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.62; H, 6.78; N, 12.30.

6-Benzyl-5-ethoxycarbonyl-1-(cyclopentylmethyl)uracil (4d)

Yield: 1.13 g (65%); light brown solid; mp 190–192 °C.

^{1}H NMR ($CDCl_3$): δ = 1.43 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.52–2.30 (m, 9 H, 4 × CH_2, CH, cyclopentyl), 3.83 (d, *J* = 7.0 Hz, 2 H, CH_2N), 4.12 (s, 2 H, C*H*$_2$Ph), 4.25 (q, *J* = 7.0 Hz, 2 H, OCH_2), 7.24–7.56 (m, 5 H, H_{arom}), 9.72 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 13.92 (CH_3), 24.56 (2 × CH_2, cyclopentyl), 30.32 (2 × CH_2, cyclopentyl), 36.10 (*C*H$_2$Ph), 40.63 (CH, cyclopentyl), 48.35 (NCH_2), 62.05 (OCH_2), 111.24 (C-5), 127.43, 127.55, 129.23, 134.08 (C_{arom}), 150.97 (C-2), 155.11 (C-6), 160.08 (C-4), 164.65 (COO).

EIMS: *m*/*z* = 356 [M^+].

Anal. Calcd for $C_{20}H_{24}N_2O_4$ 356.43: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.30; H, 6.88; N, 7.69.

6-Benzyl-5-ethoxycarbonyl-1-isopropyluracil (4e)

Yield: 1.17 g (71%); light yellow solid; mp 185–186 °C.

^{1}H NMR ($CDCl_3$): δ = 1.21 (m, 9 H, 3 × CH_3), 3.98 (s, 2 H, C*H*$_2$Ph), 4.26 (m, 3 H, OCH_2, NCH), 7.24–7.44 (m, 5 H, H_{arom}), 9.34 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 13.67 (CH_3), 19.01 (2 × CH_3), 36.84 (*C*H$_2$Ph), 52.41 (NCH), 61.98 (OCH_2), 111.00 (C-5), 127.32, 128.57, 129.74, 134.87 (C_{arom}), 150.79 (C-2), 154.67 (C-6), 160.03 (C-4), 165.06 (COO).

HRMS–MALDI: *m*/*z* [MH^+] calcd for $C_{17}H_{20}NaN_2O_4$: 339.1315; found: 339.1310.

6-Benzyl-5-ethoxycarbonyl-1-(4-methoxyphenylmethyl)uracil (4f)

Yield: 1.20 g (59%); light yellow solid; mp 143–144 °C.

^{1}H NMR (DMSO-d_6): δ = 1.25 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 4.03 (s, 2 H, C*H*$_2$Ph), 4.19 (t, *J* = 7.2 Hz, 2 H, OCH_2), 5.00 (s, 2 H, NCH_2), 7.09–7.68 (m, 9 H, H_{arom}).

^{13}C NMR (DMSO-d_6): δ = 13.64 (OCH_2CH_3), 35.31 (*C*H$_2$Ph), 45.08 (NCH_2), 55.04 (OCH_3), 61.20 (OCH_2), 110.94 (C-5), 114.19, 127.62, 127.97, 129.54, 134.48, 158.49 (C_{arom}), 150.94 (C-2), 153.51 (C-4), 159.85 (C-6), 164.39 (COO).

HRMS–MALDI: *m*/*z* [MH^+] calcd for $C_{22}H_{22}NaN_2O_5$: 417.1421; found: 417.1417.

6-Benzyl-5-allyloxycarbonyl-1-(4-methoxyphenylmethyl)uracil (4g)
Yield: 1.13 g (57%); yellow solid; mp 169–173 °C.

^{1}H NMR ($CDCl_3$): δ = 3.81 (s, 3 H, OCH_3), 3.97 (s, 2 H, CH_2Ph), 4.69 (d, *J* = 2.70 Hz, 2 H, OCH_2), 4.90 (s, 2 H, NCH_2), 5.15 (d, *J* = 7.20 Hz, 1 H, CH-allyl), 5.35 (d, *J* = 10.2 Hz, 1 H, CH-allyl), 5.88 (m, 1 H, CH-allyl), 6.89–7.48 (m, 9 H, H_{arom}), 9.62 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 35.87 (*C*H_2Ph), 46.47 (NCH_2), 55.31 (OCH_3), 66.53 (OCH_2), 111.17 (C-5), 119.13 (C-allyl), 114.55, 127.82, 128.17, 129.37, 133.93, 159.79 (C_{arom}), 131.16 (C-allyl), 151.12 (C-2), 155.64 (C-4), 159.56 (C-6), 164.10 (COO).

5-Allyloxycarbonyl-6-benzyl-1-isopropyluracil (4h)
Yield: 1.06 g (62%); orange solid; mp 170–171 °C.

^{1}H NMR ($CDCl_3$): δ = 1.16 (m, 6 H, 2 × CH_3), 4.00 (s, 2 H, CH_2Ph), 4.25 (m, 1 H, NCH), 4.78 (d, *J* = 2.7 Hz, 2 H, CH_2-allyl), 5.35 (m, 2 H, CH-allyl), 5.86 (m, 1 H, CH-allyl), 7.21–7.54 (m, 5 H, H_{arom}), 8.62 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 19.99 (2 × CH_3), 37.84 (*C*H_2Ph), 53.47 (NCH), 67.98 (OCH_2), 109.55 (C-5), 117.54 (C-allyl), 127.72, 127.97, 129.68 134.56 (C_{arom}), 131.45 (C-allyl), 150.72 (C-2), 153.97 (C-6), 160.13 (C-4), 164.87 (COO).

HRMS–MALDI: *m*/*z* [MH^+] calcd for $C_{18}H_{20}NaN_2O_4$: 351.1315; found: 351.1298.

Deprotection of 4-Methoxybenzyl Uracils; General Procedure
The 4-methoxybenzyl protected uracils **4f**,**g** were dissolved in trifluoroacetic acid and stirred at r.t. for 48 h after which the solvent was evaporated in vacuo to give an oily product. The residual material was purified by chromatography on a silica gel column with EtOAc to afford the compounds **5a**,**b**.

6-Benzyl-5-ethoxycarbonyluracil (5a)
Yield: 0.59 g (59%); light yellow solid; mp 196–198 °C.

^{1}H NMR (DMSO-d_6): δ = 1.09 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.81 (s, 2 H, CH_2Ph), 4.21 (q, *J* = 7.2 Hz, 2 H, OCH_2), 7.24–7.46 (m, 5 H, H_{arom}), 11.42 (s, 1 H, NH), 11.49 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 13.80 (CH_3), 35.75 (*C*H_2Ph), 60.72 (OCH_2), 106.09 (C-5), 126.91, 128.47, 135.79 (C_{arom}), 150.27 (C-2), 155.64 (C-4), 161.14 (C-6), 164.21 (COO).

HRMS–MALDI: *m*/*z* [MH^+] calcd for $C_{14}H_{14}NaN_2O_4$: 275.1026; found: 275.1027.

6-Benzyl-5-allyloxycarbonyluracil (5b)
Yield: 0.67g (67%); white solid; mp 157–158 °C.

^{1}H NMR (DMSO-d_6): δ = 3.87 (s, 2 H, CH_2Ph), 4.73 (d, *J* = 2.70 Hz, 2 H, OCH_2), 5.23 (d, *J* = 7.20 Hz, 1 H, CH-allyl), 5.38 (d, *J* = 10.2 Hz, 1 H, CH-allyl), 5.91 (m, 1 H, CH-allyl), 7.27–7.48 (m, 5 H, H_{arom}), 11.45 (s, 1 H, NH), 11.61 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 35.77 (*C*H_2Ph), 65.12 (OCH_2), 105.66 (C-5), 118.00 (C-allyl), 126.94, 128.57, 135.79, (C_{arom}), 132.09 (C-allyl), 150.27 (C-2), 156.33 (C-4), 161.13 (C-6), 163.99 (COO).

HRMS–MALDI: *m*/*z* [MH^+] calcd for $C_{15}H_{14}NaN_2O_4$: 309.0846; found: 309.0839.

N-1 Alkylation of 5,6-Disubstituted Uracil Derivatives; General Procedure
To a suspension of the appropriate uracil (**5a**,**b**, 2 mmol) in anhyd $CHCl_3$ was added *N*,*O*-bis(trimethylsilyl) acetamide (BSA) (5 mmol) and the stirring was continued until all the starting material had dissolved. Then (chloromethyl) ethyl ether (2 mmol) or diallyloxymethane (2 mmol) was added and the reaction mixture was stirred until TLC showed no further change in amount of starting material. After evaporation of the solvent in vacuo the product was chromatographed on a silica gel column with EtOAc–petroleum ether (1:1) as solvent to obtain the pure *N*-1 alkylated products **6a**–**c**.

6-Benzyl-5-ethoxycarbonyl-1-ethoxymethyluracil (6a)
Yield: 0.35 g (55%); white solid; mp 120–121 °C.

^{1}H NMR ($CDCl_3$): δ = 1.26 (m, 6 H, 2 × CH_3), 3.62 (q, *J* = 7.4 Hz, 2 H, OCH_2), 4.21 (s, 2 H, CH_2Ph), 4.34 (q, *J* = 7.1 Hz, 2 H, OCH_2), 5.18 (s, 2 H, NCH_2), 7.22–7.49 (m, 5 H, H_{arom}), 9.67 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 13.93 (CH_3), 14.94 (CH_3) 35.04 (*C*H_2Ph), 62.11 (OCH_2), 65.33 (OCH_2), 72.63 (NCH_2), 112.06 (C-5), 127.53, 127.95, 129.16, 134.28 (C_{arom}), 151.22 (C-2), 154.82 (C-4), 159.90 (C-6), 164.21 (COO).

HRMS–MALDI: *m*/*z* [MH^+] calcd for $C_{17}H_{20}Na_1N_2O_5$: 355.1264; found: 355.1253.

5-Allyloxycarbonyl-6-benzyl-1-ethoxymethyluracil (6b)
Yield: 0.33 g (49%); white solid; mp 208–209 °C.

^{1}H NMR ($CDCl_3$): δ = 1.21 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.61 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.27 (s, 2 H, CH_2Ph), 4.75 (d, *J* = 2.70 Hz, 2 H, OCH_2-allyl), 5.19 (s, 2 H, NCH_2), 5.21 (d, *J* =1 0.2 Hz, 1 H, CH-allyl), 5.38 (d, *J* = 16.2 Hz, 1 H, CH-allyl), 5.95 (m, 1 H, CH-allyl), 7.27–7.48 (m, 5 H, H_{arom}), 9.69 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 14.93 (CH_3), 35.02 (*C*H_2Ph), 65.35 (OCH_2), 66.56 (OCH_2-allyl), 72.48 (NCH_2), 111.70 (C-5), 119.17 (C-allyl), 127.53, 127.94, 129.18, 134.24, (C_{arom}), 131.14 (C-allyl), 151.18 (C-2), 155.26 (C-4), 159.86 (C-6), 163.95 (COO).

HRMS–MALDI: *m*/*z* [MH^+] calcd for $C_{18}H_{20}NaN_2O_5$: 367.1264; found: 367.1259.

1-(Allyloxymethyl)-6-benzyl-5-ethoxycarbonyluracil (6c)
Yield: 0.31 g (45%); white solid; mp 189–193 °C.

^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H, CH_3), 4.14 (d, *J* = 2.56 Hz, 2 H, CH_2-allyl), 4.21 (s, 2 H, CH_2Ph), 4.34 (q, *J* = 7.1 Hz, 2 H, OCH_2), 5.16 (s, 2 H, NCH_2), 5.28 (m, 2 H, 2 × CH-allyl), 5.90 (m, 1 H, CH-allyl), 7.21–7.42 (m, 5 H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 13.94 (CH_3), 35.14 (*C*H_2Ph), 62.15 (OCH_2), 70.77 (OCH_2-allyl), 72.38 (NCH_2) 112.13 (C-5), 118.08 (C-allyl), 127.91, 128.37, 129.73, 134.20 (C_{arom}), 131.19 (C-allyl), 151.14 (C-2), 154.73 (C-4), 159.81 (C-6), 164.16 (COO).

HRMS–MALDI: *m*/*z* [MH^+] calcd for $C_{18}H_{20}NaN_2O_5$: 367.1264; found: 367.1252.

Cyclopentylmethyl Amine;[21] Typical Procedure
To a cold solution (–68 °C) of cyclopentanecarbonitrile (10g, 0.105 mol) in anhyd MeOH (150 mL), Na (23 g, 1.00 mol) was added in one portion and after the initial vigorous reaction the mixture was allowed to reach r.t. within 2 h. The mixture was then refluxed for 3 h and then cooled. The mixture was diluted with sat. NaCl (300 mL) and water (300 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The organic fractions were dried over Na_2SO_4 and evaporated in vacuo to give a clear oil which was not purified any further; yield 9.83 g (94%).

^{1}H NMR ($CDCl_3$): δ = 1.45 (m, 4 H, H-3, H-6), 1.86 (m, 4 H, H-4, H-5), 1.97 (m, 1 H, H-2), 2.75 (m, 2 H, CH_2NH_2).

^{13}C NMR ($CDCl_3$): δ = 25.23 (C-4, C-5), 30.15 (C-3, C-6), 43.36 (C-2), 47.66 (C-1).

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