Monatsh Chem (2010) 141:451–459
DOI 10.1007/s00706-010-0280-x

ORIGINAL PAPER

Synthesis of uracil derivatives and their alkylation: an approach to peptide non-nucleic acid monomers

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Received: 5 July 2009 / Accepted: 23 February 2010 / Published online: 23 April 2010

Abstract N^3-substituted 5-acetyluracils derived from corresponding N^3-substituted 5-acetylcytosines are versatile functional precursors that allow the introduction of various aliphatic, aromatic, carbocyclic, and carbamoyl functionalities at N^1-position. A series of 1,3-disubstituted 5-acetyluracils were synthesized by alkylation at N^1-position. For the introduction of carbamoyl functionalities a convergent approach is studied, leading to *N*-arylacetamide derivatives; the linear approach furnished peptide non-nucleic acid monomers by replacement of active ester with amino acid esters in good yields.

Keywords Uracil · Amino acid · N^1-alkylation · Peptide non-nucleic acid monomer · Spectroscopy

Introduction

Heterocycles such as pyrimidines [1–5] and [1-2,4]triazolo[1,5-*a*]pyrimidines [6] have been the subject of chemical and biological studies due to their interesting pharmacological activities such as antipyretic [7, 8], analgesic [9, 10], anti-inflammatory [11, 12], potential herbicidal [13], fungicidal [14, 15, 16], and leishmanicidal [17, 18]. N^3-substituted 5-acetyluracils could be accessed either by cyclization of ureidomethylene-acetoacetate [19, 20] or by reaction of 1,3-oxazine-2,4-diones with amides [21]. In this work we have developed a novel route towards synthesis of uracil derivatives **2** and studied their alkylation with alkyl halide/analide/amino acids/esters. Previously we have reported the synthesis of 4-aryl/4-aminopyrimidines and studied their N^1-alkylation reactions [22, 23].

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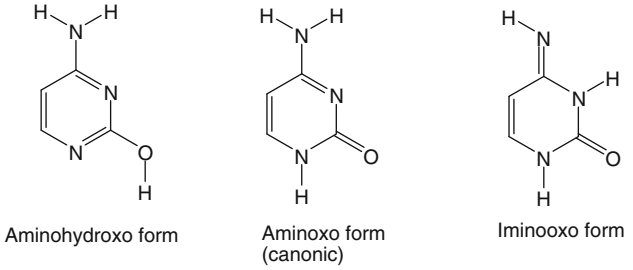
Results and discussion

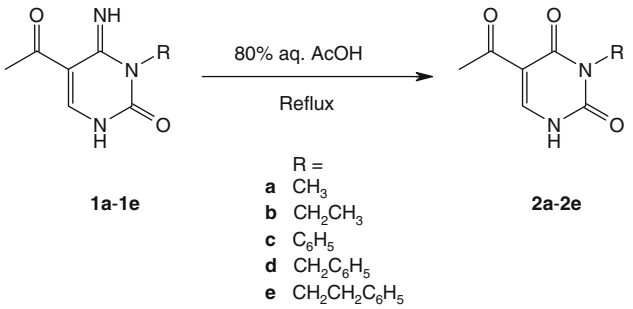
Nucleobases exist in different tautomeric forms in an equilibrium, which is strongly dependent on the interaction of these molecules with their environment [24–29]. Knowledge regarding this tautomerization in different environments can provide insight into the influence of solvent effects on molecular stability. It has also been studied experimentally [30–32] and theoretically [33–35] that cytosine exists primarily in two most stable tautomeric forms, i.e., the aminooxo form (canonic form) and aminohydroxo form. The existence of a small amount of the iminooxo form has been shown experimentally and theoretically also (Scheme 1).

In a previous communication we described preparation of cytosine derivatives **1a**–**1e** having the acetyl group at 5-position and different substituents at N^3-position [36]. In this work we decided to study the amount of the iminooxo form by converting the cytosine derivatives to uracil derivatives **2** by an acidic hydrolysis method.

Thus, the 5-acetyluracil derivatives **2a**–**2e** were obtained in 76–88% yield from corresponding 5-acetylcytosines **1a**–**1e** (Scheme 2) on treatment with 80% aqueous acetic acid at reflux temperature. Compounds **2a**–**2e** were characterized by spectral and analytical methods. As an example the ^{1}H nuclear magnetic resonance (NMR) of compound **2d** showed appearance of a D_2O exchangeable broad singlet at 12.09 ppm. Two distinct peaks at 160.9 and 150.5 ppm for two amide carbonyls and 193.3 ppm for



Scheme 1



Scheme 2

acetyl carbonyl in ^{13}C NMR confirmed the formation of uracil **2d** by hydrolysis of the corresponding cytosine **1d**. The ultraviolet (UV) spectrum showed two peaks at 405 and 385 nm. The rest of the spectral and analytical data are given in the "Experimental" section.

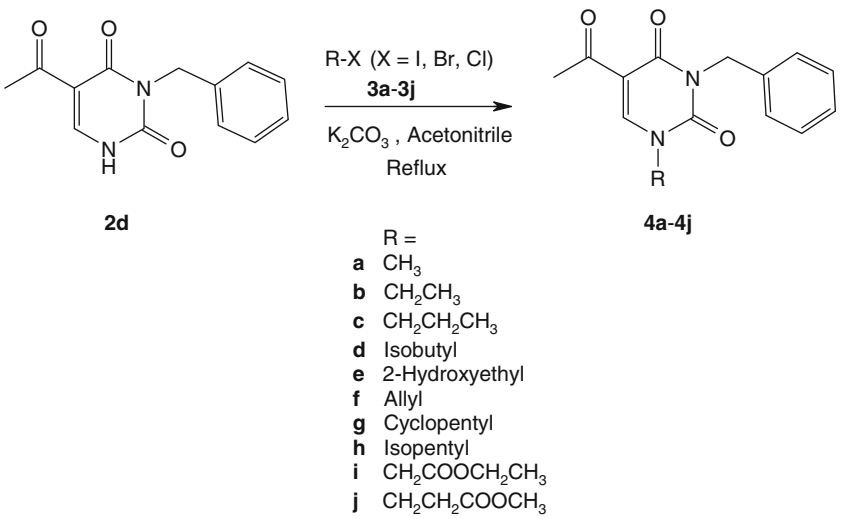
N^1-Alkyl derivatives in the uracil family are of interest because of their inherent bioactivity [37–39] or their use as starting materials for synthesis of oligonucleotides [40, 41], polymeric analogues of nucleic acids [42, 43], and non-nucleoside reverse-transcripted inhibitors [44]. However, chemoselective alkylations are a critical step and afford mixtures of N- and O-alkylated derivatives [45–48]. Much chemical effort has been applied to control N^1-regioselectivity by use of 2,4-dialkoxypyrimidines [49, 50] or their silyloxy analogues [51–53], but little attention has been given to the conditions for selective N^1-alkylation. Literature data showed that the N/O-alkylation ratio decreases with increasing hardness of the alkylating agent, supporting the hypothesis of Hard Soft Acids and Bases (HSAB) [54, 55] control in the N/O-chemoselection. Therefore we felt that the HSAB principle could be used to drive the N^1-chemoselectivity in uracil in the presence of a mild base. The generated uracil anion can be considered as an ambident nucleophile operating in a polar aprotic solvent (MeCN or *N*,*N*-dimethylformamide (DMF)). The N^1 atom is softer than the oxygen atom and attacks the soft carbon atom of the alkylating agent in an S_N2 mechanism. It was noted [56–58] that uracils with a carbonyl group at N^1-position and benzyl at N^3-position showed remarkable biological activities. Hence we have chosen **2d** for alkylation reactions. Thus compound **2d** was reacted with alkyl halides to obtain N^1-substituted compounds **4a–4j** (Scheme 3) in refluxing acetonitrile using a mildly basic medium in 75–90% yield. Compounds **4a–4j** were characterized by infrared (IR), ^1H and ^{13}C NMR, and elemental analysis. It was found that the broad singlet present in compound **2d** for NH proton at 12.0 ppm disappeared, and the presence of two signals at 160.5 and 150.5 ppm for amide carbonyls and one acetyl carbonyl carbon at 193.5 ppm indicated that only N-alkylated product was obtained under these conditions.

The introduction of a carbamoyl functionality at N^1-position was achieved by alkylation of **2d** with 2-bromo-*N*-arylacetamide. Thus, compounds **6a–6g** were obtained by treating **2d** with 2-bromo-*N*-arylacetamides **5a–5g** in presence of a mild base in an aprotic polar solvent such as DMF in 75–95% yield (Scheme 4). Some workers have noted O-alkylation in carbostyrils [59] under these reaction conditions using crown ethers as phase-transfer catalyst. It was also observed that, on substitution at N^1-position, the UV maximum was shifted to 292 nm when compound **2d** was substituted with a 2-methylpropyl moiety (compound **4d**), whereas substitution at N^1-position with *N*-arylacetamides showed an UV absorption peak at 286 nm (compound **6f**).

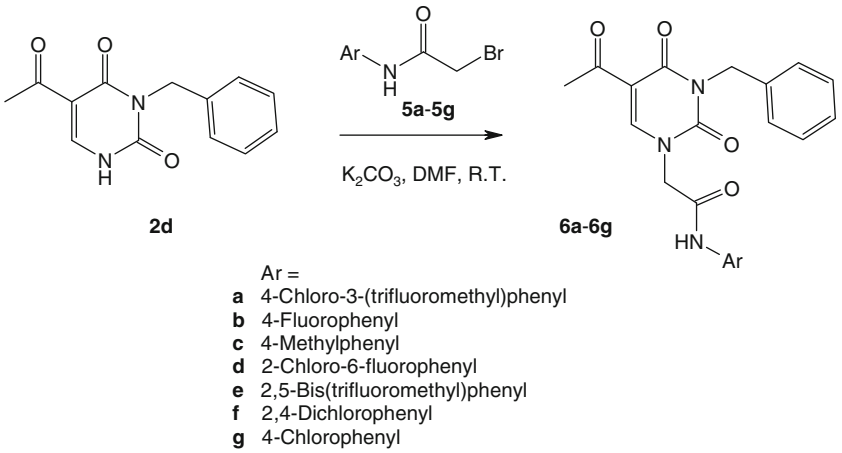
Uracil derivative **2d** was further *N*-linked with amino acid esters **10a–10d**. This involved a multistep synthesis of **11** (Scheme 5). Thus, compound **2d** was reacted with ethyl 2-bromoacetate to obtain compound **7**, which on basic hydrolysis yielded acid **8**. Compound **8** was then transformed into an active ester **9** using *N*-hydroxysuccinimide in presence of a dehydrating agent such as *N*,*N*′-dicylohexylcarbodiimide (DCC). Replacement of the active ester with ethyl esters of amino acids **10a–10d** in refluxing Tetrahydrofuran (THF) furnished the desired key intermediates of peptide non-nucleic acid monomers **11a–11d** in 60–65% yield. The uracils substituted by amino acids at N^1-position have been reported by Dewar et al. [60, 61], however their uracils are different from ours. Alternatively compounds **11** were synthesized directly by base-catalyzed condensation of **8** with ethyl esters of corresponding amino acids using *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (TBTU) as peptide coupling reagent in 75–80% yield.

The latter approach is advantageous as TBTU serves the purpose of in situ active ester formation and dehydration. Both unreacted (if any) compounds (**2d** or **10a–10d**) can be safely removed by acidic or basic washing along with the byproduct urea giving the pure key intermediates of peptide nucleic acids with superior yields at lower temperature and lesser reaction time. All compounds **11a–11d** were characterized by spectral and analytical methods.

Scheme 3



Scheme 4



Conclusion

We have reported a simple and convenient method to synthesize some novel uracil derivatives. This transformation could be of importance to synthetic and combinatorial chemists to generate an interesting library of substituted uracils which could exhibit applications in pharmacological activities.

Experimental

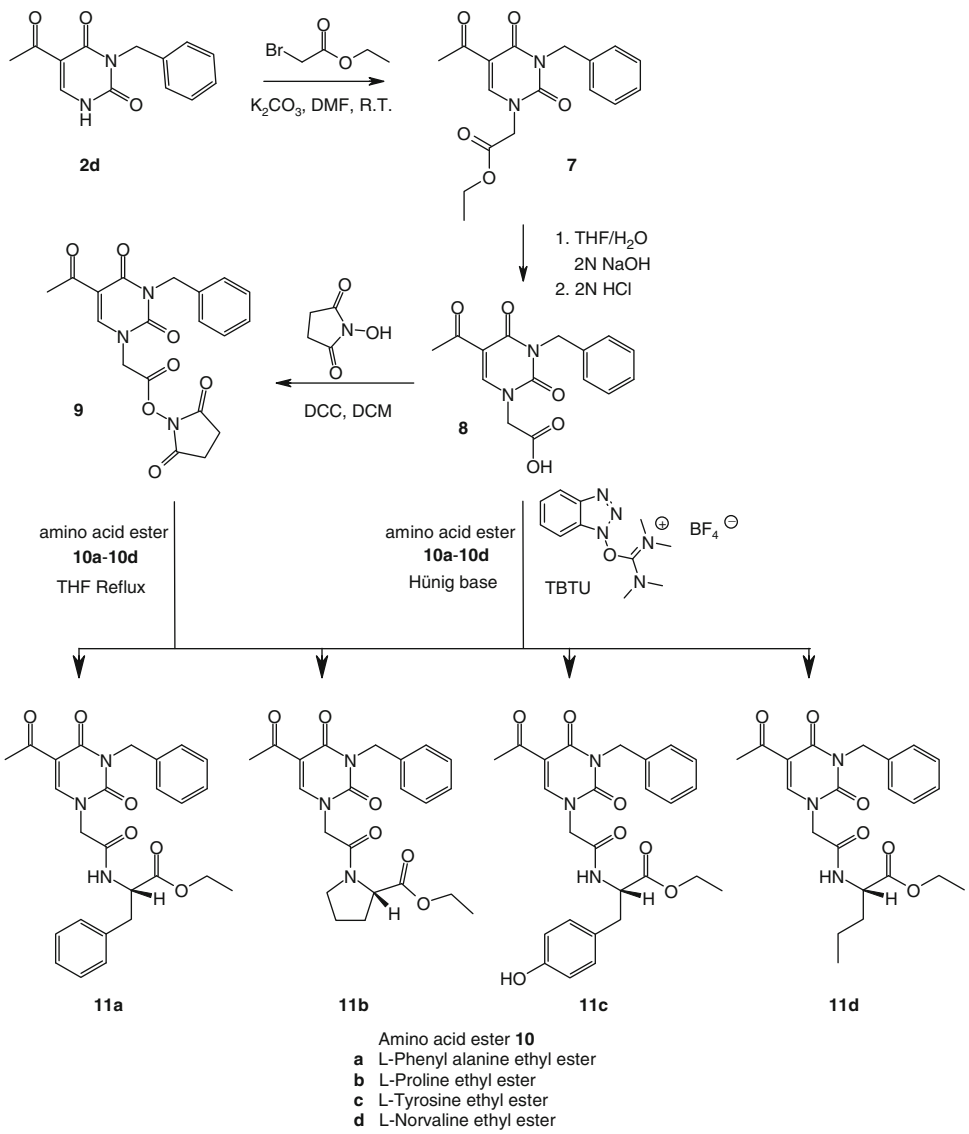
Melting points: Gallenkamp melting point apparatus. IR spectra (KBr-compression mould): Shimadzu IR-408; ^{1}H NMR (300 MHz). ^{13}C-NMR (75 MHz) spectra: Varian XL-300, dimethyl sulfoxide (DMSO)-d_6, $CDCl_3$, tetramethylsilane (TMS). Mass spectra: Shimadzu GC–MS QP 2010A mass-spectral instrument with ionization potential of 70 eV. Elemental analyses (C, H, N, S) were conducted using the HOSLI CH-Analyzer; the results were in agreement with calculated values.

*General procedure for synthesis of **2a–2e***

A magnetically stirred solution of **1** (4.12 mmol) in 10 cm^3 80% aqueous acetic acid was heated to 110 °C and maintained for 20–25 h [thin-layer chromatography (TLC) check, $CHCl_3$:MeOH 9:1]. The reaction mixture was then filtered through Celite, evaporated completely, and triturated with diisopropylether. The solid residue was recrystallized from ethanol to give **2** as pale yellow solids in 76–88% yield.

5-Acetyl-3-methylpyrimidine-2,4(1H,3H)-dione (**2a**, $C_7H_8N_2O_3$)
Yield 88%; m.p.: 218–220 °C; IR (KBr): $\bar{\nu}$ = 3,325, 1,711, 1,667, 1,605 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 11.89 (bs, 1H, NH), 8.19 (s, 1H, C_6H), 3.22 (s, 3H, N–CH_3), 2.41 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 195.3, 164.2,

Scheme 5



159.3, 157.1, 154.6, 99.2, 29.4, 26.1 ppm; EIMS: *m/z* (%) = 168 (M^+, 12), 152 (3), 139 (4), 124 (6), 110 (18), 95 (12), 57 (19), 44 (100).

5-Acetyl-3-ethylpyrimidine-2,4(1H,3H)-dione
(**2b**, $C_8H_{10}N_2O_3$)
Yield 76%; m.p.: 266–268 °C; IR (KBr): $\bar{\nu}$ = 3,282, 1,723, 1,666, 1,612 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 11.85 (bs, 1H, NH), 8.24 (s, 1H, C_6H), 3.93 (q, 2H, J = 6.8 Hz, CH_2), 2.42 (s, 3H, CH_3), 1.10 (t, 3H, J = 6.8 Hz, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 195.3, 157.1, 154.6, 140.1, 119.2, 38.4, 26.1, 15.0 ppm; EIMS: *m/z* (%) = 182 (M^+, 17), 153 (23), 138 (25), 83 (38), 43 (58), 31 (100).

5-Acetyl-3-phenylpyrimidine-2,4(1H,3H)-dione
(**2c**, $C_{12}H_{10}N_2O_3$)
Yield 85%; m.p.: 145–147 °C; IR (KBr): $\bar{\nu}$ = 3,285, 1,711, 1,667,1,615, 1,561 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 12.82 (bs, 1H, NH), 7.82 (s, 1H, C_6H), 7.37–7.14 (m, 5H, Ar–H), 2.42 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 198.3, 165.2, 150.2, 140.1, 134.2, 131.2, 130.2, 125.1, 119.4, 115.2, 26.5 ppm; EIMS: *m/z* (%) = 230 (M^+, 9), 186 (2), 137 (4), 119 (100), 110 (25), 77 (32), 44 (9).

5-Acetyl-3-benzylpyrimidine-2,4(1H,3H)-dione
(**2d**, $C_{13}H_{12}N_2O_3$)
Yield 84%; m.p.: 156–158 °C; IR (KBr): $\bar{\nu}$ = 3,134, 1,724, 1,671, 1,608, 1,575 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 12.09 (bs, 1H, NH), 8.10 (s, 1H, C_6H), 7.29–7.25 (m, 5H, Ar–H), 4.97 (s, 2H, N–CH_2), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.3, 160.9, 150.5, 146.8, 136.7, 128.2, 127.4, 127.0, 110.6, 43.1, 30.2 ppm; EIMS: *m/z* (%) = 244 (M^+, 33), 153 (3), 132 (26), 106 (15), 91 (100), 70 (28), 65 (23), 43 (34), 31 (52).

5-Acetyl-3-(2-phenylethyl)pyrimidine-2,4(1H,3H)-dione (**2e**, $C_{14}H_{14}N_2O_3$)
Yield 81%; m.p.: 172–175 °C; IR (KBr): $\bar{\nu}$ = 3,190, 1,726, 1,685, 1,635, 1,434 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 11.98 (bs, 1H, NH), 8.05 (s, 1H, C_6H), 7.28–7.21 (m, 5H, Ar–H), 3.99 (t, 2H, J = 6.0 Hz, NCH_2), 2.82 (t, 2H, J = 6.0 Hz, CH_2), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.5, 160.8, 150.3, 146.5, 138.4, 128.5, 128.4, 126.3, 110.6, 41.3, 33.0, 30.3 ppm; EIMS: *m/z* (%) = 258 (M^+, 5), 138 (3), 104 (100), 91 (9), 82 (5), 65 (5), 43 (9).

General procedure for synthesis of ***4a–4j***

To a suspension of 0.2 g **2d** (0.82 mmol) and 0.135 g anhydrous potassium carbonate (0.98 mmol) in 10 cm^3 acetonitrile, **3** (0.85 mmol) was added at room temperature and refluxed for 6–8 h (TLC check, $CHCl_3$:MeOH, 9.5:0.5). The reaction mixture was then filtered through Celite, and the filtrate was evaporated completely. The solid residue was recrystallized from ethanol to give **4a**–**4h** as colorless crystals in 75–90% yield. It was observed that compounds **4i** and **4j** were obtained as oils which solidified on standing.

5-Acetyl-3-benzyl-1-methylpyrimidine-2,4(1H,3H)-dione (**4a**, $C_{14}H_{14}N_2O_3$)
Yield 88%; m.p.: 123–125 °C; IR (KBr): $\bar{\nu}$ = 1,733, 1,665, 1,622, 1,612, 1,558 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.51 (s, 1H, C_6H), 7.32 (m, 5H, Ar–H), 5.05 (s, 2H, N–CH_2), 3.41 (s, 3H, N–CH_3), 2.51 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.3, 161.2, 152.6, 137.2, 128.5, 110.2, 44.2, 37.4, 30.1 ppm; EIMS: *m/z* (%) = 258 (M^+, 25), 243 (10), 167 (5), 153 (3), 126 (16), 104 (6), 91 (100), 77 (12), 65 (18), 42 (23).

5-Acetyl-3-benzyl-1-ethylpyrimidine-2,4(1H,3H)-dione (**4b**, $C_{15}H_{16}N_2O_3$)
Yield 70%; m.p.: 96–98 °C; IR (KBr): $\bar{\nu}$ = 1,734, 1,662, 1,622, 1,605, 1,561 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.52 (s, 1H, C_6H), 7.31 (m, 5H, Ar–H), 5.03 (s, 2H, N–CH_2), 3.93 (q, 2H, J = 6.4 Hz, N–CH_2), 2.51 (s, 3H, CH_3), 1.23 (t, 3H, J = 6.4 Hz, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.4, 160.6, 150.3, 136.7, 128.3, 110.8, 45.2, 43.8, 30.2, 14.0 ppm; EIMS: *m/z* (%) = 272 (M^+, 40), 257 (12), 243 (7), 167 (5), 132 (18), 98 (20), 91 (100), 77 (15), 65 (20), 43 (30).

5-Acetyl-3-benzyl-1-propylpyrimidine-2,4(1H,3H)-dione (**4c**, $C_{16}H_{18}N_2O_3$)
Yield 75%; m.p.: 108–110 °C; IR (KBr): $\bar{\nu}$ = 1,732, 1,664, 1,624, 1,612, 1,559 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.50 (s, 1H, C_6H), 7.32 (m, 5H, Ar–H), 5.00 (s, 2H, N–CH_2), 3.83 (t, 2H, J = 6.4 Hz, N–CH_2), 2.51 (s, 3H, CH_3), 1.74 (m, 2H, CH_2), 0.90 (t, 3H, J = 6.4 Hz, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.5, 160.5, 150.4, 136.8, 127.5, 110.7, 51.2, 43.9, 30.3, 21.7, 10.5 ppm; EIMS: *m/z* (%) = 286 (M^+, 26), 271 (11), 243 (2), 195 (3), 154 (14), 132 (15), 112 (11), 91 (100), 77 (13), 65 (23), 43 (28).

5-Acetyl-3-benzyl-1-(2-methylpropyl)pyrimidine-2,4(1H,3H)-dione (**4d**, $C_{17}H_{20}N_2O_3$)
Yield 83%; m.p.: 92–94 °C; IR (KBr): $\bar{\nu}$ = 1,731, 1,669, 1,627, 1,605, 1,559 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.49 (s, 1H, C_6H), 7.33 (m, 5H, Ar–H), 5.00 (s, 2H, N–CH_2), 3.72 (d, 2H, J = 6.2 Hz, N–CH_2), 2.50 (s, 3H, CH_3), 1.92 (m, 1H, CH), 0.81 (d, 6H, J = 6.8 Hz, $2CH_3$) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.5, 160.5, 150.5, 136.8, 127.4, 110.6, 56.2, 43.9, 30.3, 27.5, 19.2 ppm; EIMS: *m/z* (%) = 300 (M^+, 80), 285 (15), 244 (10), 168 (17), 124 (20), 106 (28), 91 (100), 82 (18), 65 (18), 41 (30).

5-Acetyl-3-benzyl-1-(2-hydroxyethyl)pyrimidine-2,4(1H,3H)-dione (**4e**, $C_{15}H_{16}N_2O_4$)
Yield 79%; m.p.: 130–132 °C; IR (KBr): $\bar{\nu}$ = 1,733, 1,667, 1,625, 1,602, 1,556 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.40 (s, 1H, C_6H), 7.30 (m, 5H, Ar–H), 5.00 (s, 2H, N–CH_2), 3.91 (bs, 2H, O–CH_2), 3.60 (bs, 2H, N–CH_2), 2.52 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.5, 160.7, 151.3, 136.7, 127.6, 110.0, 58.2, 52.3, 43.9, 30.3 ppm; EIMS: *m/z* (%) = 288 (M^+, 28), 273 (11), 156 (4), 132 (15), 124 (11), 106 (9), 91 (100), 82 (13), 65 (18), 43 (32).

5-Acetyl-3-benzyl-1-(2-propenyl)pyrimidine-2,4(1H,3H)-dione (**4f**, $C_{16}H_{16}N_2O_3$)
Yield 88%; m.p.: 84–86 °C; IR (KBr): $\bar{\nu}$ = 1,735, 1,657, 1,624, 1,612, 1,566 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.40 (s, 1H, C_6H), 7.30 (m, 5H, Ar–H), 5.90 (m, 1H, CH), 5.20 (m, 2H, olefinic CH_2), 5.00 (s, 2H, N–CH_2), 4.53 (m, 2H, N–CH_2), 2.52 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.5, 160.5, 150.3, 149.9, 136.6, 132.4, 127.5, 118.4, 111.0, 51.2, 43.9, 30.3 ppm; EIMS: *m/z* (%) = 284 (M^+, 29), 269 (6), 243 (3), 200 (5), 171 (2), 152 (11), 138 (34), 110 (10), 91 (100), 77 (15), 65 (31), 41 (36).

5-Acetyl-3-benzyl-1-cyclopentylpyrimidine-2,4(1H,3H)-dione (**4g**, $C_{18}H_{20}N_2O_3$)
Yield 87%; m.p.: 94–96 °C; IR (KBr): $\bar{\nu}$ = 1,734, 1,668, 1,622, 1,602, 1,566 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.31 (s, 1H, C_6H), 7.31 (m, 5H, Ar–H), 5.00 (s, 2H, N–CH_2), 4.80 (m, 1H, CH), 2.50 (s, 3H, CH_3), 2.00 (m, 2H, CH_2), 1.82 (m, 4H, $2CH_2$), 1.63 (m, 2H, CH_2) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.4, 160.2, 150.4, 147.0, 136.7, 127.6, 110.9, 59.8, 44.0, 30.5, 30.2, 23.6 ppm; EIMS: *m/z* (%) = 312 (M^+, 27), 244 (23), 229 (8), 202 (12), 180 (3), 153 (5), 132 (15), 112 (14), 106 (28), 91 (100), 65 (17), 41 (36).

5-Acetyl-3-benzyl-1-(3-methylbutyl)pyrimidine-2,4(1H,3H)-dione (**4h**, $C_{18}H_{22}N_2O_3$)
Yield 84%; m.p.: 98–100 °C; IR (KBr): $\bar{\nu}$ = 1,731, 1,667, 1,625, 1,602, 1,556 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.51 (s, 1H, C_6H), 7.30 (m, 5H, Ar–H), 5.01 (s, 2H, N–CH_2), 3.90 (t, 2H, J = 5.4 Hz, N–CH_2), 2.51 (s, 3H, CH_3), 1.52 (m, 3H, CH and CH_2), 0.90 (d, 6H, J = 6.2 Hz, $2CH_3$) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.5, 160.5, 150.5, 150.2, 136.7, 127.5, 110.8, 48.3, 43.9, 37.2, 30.3, 25.2, 22.2 ppm; EIMS: *m/z* (%) = 314 (M^+, 33), 299 (9), 258 (3), 223 (27), 205 (6), 182 (8), 132 (10), 106 (14), 91 (100), 65 (12), 41 (22).

Ethyl 2-(5-acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)acetate (**4i**, $C_{17}H_{18}N_2O_5$)
Yield 92%; m.p.: 32–34 °C; IR (KBr): $\bar{\nu}$ = 1,733, 1,667, 1,625, 1,602, 1,558 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.51 (s, 1H, C_6H), 7.36–7.15 (m, 5H, Ar–H), 5.20 (s, 2H, N–CH_2), 4.63 (s, 2H, N–CH_2), 4.17 (q, 2H, J = 6.2 Hz, O–CH_2), 2.41 (s, 3H, CH_3), 1.22 (t, 3H, J = 6.2 Hz, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 194.4, 167.3, 160.3, 153.3, 149.9, 145.9, 136.9, 128.2, 127.8, 108.7, 62.5, 50.3, 44.8, 26.8, 14.3 ppm; EIMS: *m/z* (%) = 330 (M^+, 12), 315 (3), 198 (4), 132 (17), 91 (100), 65 (18), 43 (27).

Methyl 3-(5-acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)propionate (**4j**, $C_{17}H_{18}N_2O_5$)
Yield 95%; m.p.: 32–35 °C (*n*-pentane); IR (KBr): $\bar{\nu}$ = 1,735, 1,662, 1,635, 1,612, 1,548 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 8.50 (s, 1H, C_6H), 7.36–7.15 (m, 5H, Ar–H), 5.21 (s, 2H, N–CH_2), 3.99 (t, 2H, J = 6.0 Hz, N–CH_2), 3.66 (s, 3H, O–CH_3), 2.80 (t, 2H, J = 6.0 Hz, CH_2), 2.40 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.4, 171.3, 160.3, 153.4, 149.2, 145.7, 136.3, 128.4, 127.2, 108.5, 62.5, 50.3, 41.6, 33.4, 30.2 ppm; EIMS: *m/z* (%) = 330 (M^+, 28), 315 (5), 244 (58),198 (5), 153 (5),132 (28),112 (14), 91 (100), 65 (15), 43 (24).

General procedure for synthesis of ***6a–6g***

To a suspension of 0.5 g **2d** (2.1 mmol) and 0.3 g anhydrous potassium carbonate (2.1 mmol) in 10 cm^3 DMF, **5** (2.2 mmol) was added and stirred for 2–3 h at room temperature (TLC check, $CHCl_3$:MeOH, 9:1). The reaction mixture was then quenched in ice-cold water, and the precipitated solid was filtered off, washed with water, dried, and recrystallized from DMF:H_2O 1:5 to give **6a–6g** as a white solids in 70–95% yield.

2-(5-Acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-N-[4-chloro-3-(trifluoromethyl)phenyl]acetamide (**6a**, $C_{22}H_{17}ClF_3N_3O_4$)
Yield 82%; m.p.: 197–199 °C; IR (KBr): $\bar{\nu}$ = 3,268, 1,723, 1,696, 1,658, 1,597, 1,545 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 10.85 (bs, 1H, NH), 8.59 (s, 1H, C_6H), 8.15 (d, 1H, J = 3.0 Hz, Ar–H), 7.78 (dd, 1H, J = 3.0, 3.0 Hz, Ar–H), 7.70 (d, 1H, J = 9.0 Hz, Ar–H), 7.29 (m, 5H, Ar–H), 5.03 (s, 2H, CH_2), 4.83 (s, 2H, N–CH_2), 2.32 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.4, 165.7, 160.4, 151.3, 150.5, 137.7, 132.2, 128.2, 127.4, 126.9, 124.3, 123.8, 120.7, 117.6, 110.7, 52.1, 44.0, 30.5 ppm; EIMS: *m/z* (%) = 481 (M + 2, 5), 479 (M^+, 15), 285 (22), 257 (14), 132 (12), 124 (33), 91 (100), 82 (21), 65 (7), 43 (17).

2-(5-Acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-N-(4-fluorophenyl)acetamide
(**6b**, $C_{21}H_{18}FN_3O_4$)
Yield 83%; m.p.: 265–267 °C; IR (KBr): $\bar{\nu}$ = 3,266, 1,718, 1,697, 1,657, 1,602, 1,542 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 10.45 (bs, 1H, NH), 8.55 (s, 1H, C_6H), 7.56 (m, 2H, Ar–H), 7.25 (m, 7H, Ar–H), 5.01 (s, 2H, N–CH_2), 4.77 (s, 2H, N–CH_2), 2.49 (s, 3H, –CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.7, 164.9, 160.9, 159.8, 156.6, 151.5, 150.6, 136.5, 134.8, 128.4, 127.5, 121.0, 115.7, 110.7, 52.1, 44.2, 30.6 ppm; EIMS: *m/z* (%) = 395 (M^+, 11), 285 (14), 257 (9), 152 (7), 132 (7), 124 (35), 111 (11), 91 (87), 82 (17), 65 (8), 44 (25), 32 (100).

2-(5-Acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-N-(4-methylphenyl)acetamide
(**6c**, $C_{22}H_{21}N_3O_4$)
Yield 88%; mp 261–263 °C; IR (KBr): $\bar{\nu}$ = 3,274, 1,725, 1,691, 1,654, 1,591, 1,536 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 10.27 (bs, 1H, NH), 8.56 (s, 1H, C_6H), 7.28 (d, 2H, J = 5.4 Hz, Ar–H), 7.28 (m, 5H, Ar–H), 7.12 (d, 2H, J = 8.4 Hz, Ar–H), 5.02 (s, 2H, CH_2), 4.78 (s, 2H, N–CH_2), 2.48 (s, 3H, CH_3), 2.24 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.4, 164.5, 160.4, 151.4, 150.5, 136.4, 135.8, 132.5, 129.1, 128.2, 127.4, 118.9, 110.5, 51.9, 44.0, 30.5, 20.5 ppm; EIMS: *m/z* (%) = 391 (M^+, 12), 285 (10), 257 (6), 124 (39), 107 (58), 91 (100), 82 (18), 65 (8), 43 (15).

2-(5-Acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-N-(2-chloro-6-fluorophenyl)acetamide
(**6d**, $C_{21}H_{17}ClFN_3O_4$)
Yield 96%; m.p.: 275–277 °C; IR (KBr): $\bar{\nu}$ = 3,118, 1,715, 1,695, 1,654, 1,611, 1,538 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 10.22 (bs, 1H, NH), 8.63 (s, 1H, C_6H), 7.46 (m, 8H, Ar–H), 5.04 (s, 2H, CH_2), 4.91 (s, 2H, N–CH_2), 2.48 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.4, 165.3, 160.4, 151.3, 136.4, 130.9, 128.8, 127.4, 125.7, 115.4, 110.6, 51.7, 44.0, 30.5 ppm; EIMS: *m/z* (%) = 431 (M + 2, 4), 429 (M^+, 12), 285 (24), 257 (15), 132 (12), 124 (37), 91 (100), 82 (23), 65 (8), 43 (18).

2-(5-Acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-N-[2,5-bis(trifluoromethyl)phenyl]acetamide
(**6e**, $C_{23}H_{17}F_6N_3O_4$)
Yield 74%; m.p.: 224–226 °C; IR (KBr): $\bar{\nu}$ = 3,288, 1,712, 1,690, 1,655, 1,591, 1,534 cm^{-1}; ^1H NMR (DMSO-d_6):

$\delta = 10.32$ (bs, 1H, NH), 8.59 (s, 1H, C_6H), 8.02 (d, $J = 9.0$ Hz, 1H, Ar–H), 7.91 (s, 1H, Ar–H), 7.85 (d, $J = 9.0$ Hz, 1H, Ar–H), 7.28 (m, 5H, Ar–H), 5.04 (s, 2H, CH_2), 4.90 (s, 2H, N–CH_2), 2.50 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 193.4$, 166.8, 160.4, 151.4, 150.5, 136.5, 135.6, 133.1, 128.2, 127.7, 125.8, 124.8, 123.4, 121.1, 120.7, 110.6, 51.8, 44.0, 30.5 ppm; EIMS: *m/z* (%) = 513 (M^+, 28), 498 (2), 285 (6), 257 (9), 132 (24), 124 (37), 91 (100), 82 (27), 65 (9), 43 (22).

2-(5-Acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-N-(2,4-dichlorophenyl)acetamide
(**6f**, $C_{21}H_{17}Cl_2N_3O_4$)
Yield 91%; m.p.: 254–256 °C; IR (KBr): $\bar{\nu} = 3{,}285$, 1,722, 1,687, 1,645, 1,581, 1,531 cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 10.11$ (bs, 1H, NH), 8.60 (s, 1H, C_6H), 7.75 (m, 2H, Ar–H), 7.40 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.28 (m, 5H, Ar–H), 5.03 (s, 2H, CH_2), 4.91 (s, 2H, N–CH_2), 2.51 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 193.3$, 165.8, 160.4, 151.4, 136.4, 133.3, 129.4, 128.9, 127.4, 126.7, 110.6, 51.9, 44.0, 30.5 ppm; EIMS: *m/z* (%) = 449 (M + 4, 9), 447 (M + 2, 4), 445 (M^+, 13), 285 (32), 257 (20), 132 (18), 124 (39), 110 (5), 91 (100), 82 (20), 65 (8), 43 (11).

2-(5-Acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-N-(4-chlorophenyl)acetamide
(**6g**, $C_{21}H_{18}ClN_3O_4$)
Yield 92%; m.p.: 233–235 °C; IR (KBr): $\bar{\nu} = 3{,}281$, 1,724, 1,698, 1,659, 1,593, 1,529 cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 10.50$ (bs, 1H, NH), 8.57 (s, 1H, C_6H), 7.57 (d, 2H, $J = 6.6$ Hz, Ar–H), 7.38 (d, 2H, $J = 6.8$ Hz, Ar–H), 7.28 (m, 5H, Ar–H), 5.02 (s, 2H, -CH_2), 4.78 (s, 2H, N–CH_2), 2.48 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 193.4$, 165.0, 165.0, 160.4, 151.4, 150.4, 137.3, 136.4, 127.5, 120.5, 110.6, 52.1, 44.0, 30.5 ppm; EIMS: *m/z* (%) = 413 (M + 2, 3), 411 (M^+, 9), 285 (12), 257 (5), 127 (11), 124 (39), 110 (6), 91 (100), 82 (16), 65 (7), 43 (13).

Ethyl 2-(5-acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)acetate (**7**, $C_{17}H_{18}N_2O_5$)
To a suspension of 5 g **2d** (0.20 mol) and 3.3 g anhydrous potassium carbonate (0.024 mol) in 100 cm^3 DMF, 4.0 g ethyl 2-bromoacetate (0.024 mol) was added and stirred for 3 h at room temperature (TLC check, $CHCl_3$:MeOH, 9:1). The reaction mixture was then quenched in ice-cold water and extracted twice with 50 cm^3 ethyl acetate. The ethyl acetate layer was washed with saturated sodium chloride solution and dried over sodium sulfate. The solvent was evaporated under reduced pressure. On trituration in *n*-pentane at 5–10 °C a white precipitate was obtained, filtered, and dried under reduced pressure. Yield 92%; m.p.: 32–34 °C; IR (KBr): $\bar{\nu} = 1{,}733$, 1,667, 1,625, 1,602, 1,558 cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 8.52$ (s, 1H, C_6H), 7.36–7.15 (m, 5H, Ar–H), 5.22 (s, 2H, N–CH_2), 4.63 (s, 2H, N–CH_2), 4.17 (q, 2H, $J = 6.4$ Hz, O–CH_2), 2.41 (s, 3H,CH_3), 1.23 (t, 3H, $J = 6.4$ Hz, CH_3) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 194.4$, 167.3, 160.3, 153.3, 149.9, 145.9, 136.9, 128.2, 127.8, 108.7, 62.5, 50.3, 44.8, 26.8, 14.3 ppm; EIMS: *m/z* (%) = 330 (M^+, 12), 315 (3), 198 (4), 132 (17), 91 (100), 65 (18), 43 (27).

2-(5-Acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)acetic acid (**8**, $C_{15}H_{14}N_2O_5$)
Compound **7** (6.4 g, 0.19 mol) was dissolved in 65 cm^3 tetrahydrofuran and treated with 11.6 cm^3 2 N NaOH solution (0.23 mol). The reaction mixture was heated to 50 °C for 4–5 h (TLC check, $CHCl_3$:MeOH, 9:1), and tetrahydrofuran was evaporated under reduced pressure. The aqueous residue was acidified with 2 N HCl to pH 1–2. The product was extracted twice with 25 cm^3 ethyl acetate; washed with saturated sodium chloride solution, the extracts were dried over sodium sulfate, filtered, and evaporated under reduced pressure to obtain a colorless solid. Yield 90%; m.p.: 35–37 °C; IR (KBr): $\bar{\nu} = 3{,}542$, 1,725, 1,635, 1,619, 1,612, 1,514 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 8.80$ (s, 1H, C_6H), 7.36–7.15 (m, 5H, Ar–H), 5.20 (s, 2H, N–CH_2), 4.62 (s, 2H, N–CH_2), 2.43 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 195.8$, 168.4, 154.8, 152.1, 148.5, 135.3, 127.8, 104.4, 59.4, 50.8, 44.7, 30.7, 27.0 ppm; EIMS: *m/z* (%) = 302 (M^+, 12), 287 (3), 170 (5), 132 (12), 106 (8), 91 (70), 82 (14), 65 (17), 43 (100), 31 (65).

2,5-Dioxo-1-pyrrolidinyl 2-(5-acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)acetate (**9**, $C_{19}H_{17}N_3O_7$)
N-Hydroxysuccinimide (0.41 g, 3.6 mmol) was added slowly under stirring to a solution of 1.0 g **8** (3.3 mmol) in 20 cm^3 dry tetrahydrofuran at 0 °C. Then a solution of 0.74 g *N,N*'-dicylohexylcarbodiimide (3.6 mmol) in 5 cm^3 dichloromethane was added at 0–5 °C dropwise under stirring, which formed white crystalline *N,N*′-dicyclohexylurea. The mixture was stirred at 0–5 °C for 14–15 h and then filtered to remove the urea byproduct. The filtrate was evaporated completely and redissolved in dichloromethane. The solution was again filtered to remove the insoluble material and evaporated completely to obtain a viscous oil, which was purified by column chromatography, eluting with dichloromethane. The desired fractions were collected and evaporated under reduced pressure to obtain a colorless solid. Yield 35%; m.p.: 32–35 °C; IR (KBr): $\bar{\nu} = 1{,}815$, 1,786, 1,747, 1,663, 1,623, 1,597 cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 7.62$ (s, 1H, C_6H), 7.33 -7.21 (m, 5H, Ar–H), 5.31 (s, 2H, N–CH_2), 4.53 (s, 2H, N–CH_2), 3.80 (s, 4H, 2CH_2), 2.31 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 194.5$, 167.8, 153.3, 149.9, 145.9, 136.8, 128.2, 108.7, 53.2, 50.1, 44.8, 26.7 ppm; EIMS: *m/z* (%) = 399 (M^+, 2), 181 (8),

157 (4), 144 (28), 115 (19), 106 (22), 91 (100), 77 (16), 65 (17).

*General procedure for synthesis of **11a–11d***

Method A

To a suspension of 0.5 g **8** (0.002 mol) and 0.64 g TBTU (0.002 mol) in 20 cm^3 dichloromethane, **10** (0.002 mol) was added at room temperature. To this was added a solution of 0.774 g *N*,*N*-diisopropylethylamine (0.006 mol) in 10 cm^3 dichloromethane dropwise at room temperature. The reaction mixture was stirred for 2 h (TLC check, $CHCl_3$:MeOH, 8:2). The reaction mass was then washed twice with 20 cm^3 water followed by 20 cm^3 1% phosphoric acid, 20 cm^3 saturated sodium bicarbonate solution, and finally with 20 cm^3 saturated sodium chloride solution. The dichloromethane layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure to obtain **11** in 78–90% yield.

Method B

To a suspension of 0.2 g **9** (0.5 mmol) in 10 cm^3 tetrahydrofuran, **10** (0.55 mmol) was added and stirred at reflux temperature for 6–8 h (TLC check, $CHCl_3$:MeOH, 8:2). The reaction mixture was filtered through Celite, the filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography eluting with dichloromethane to furnish **11** in 60–65% yield.

Ethyl 2-[[2-(5-acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-1-oxoethyl]amino]-3-phenylpropionate (**11a**, $C_{26}H_{27}N_3O_6$)

Method A: yield 83%; method B: 7 h reflux, yield 62%; m.p.: 36–38 °C; IR (KBr): $\bar{\nu}$ = 3,266, 1,736, 1,697, 1,666, 1,622, 1,605, 1,548 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 10.50 (bs, 1H, NH), 8.62 (s, 1H, C_6H), 7.33 (m, 5H, Ar–H), 7.10 (m, 5H, Ar–H), 5.03 (s, 2H, N–CH_2), 4.82 (s, 2H, N–CH_2), 4.72 (dd, 1H, J = 8.4, 8.0 Hz, CH), 4.20 (q, J = 7.1 Hz, 2H, ester O–CH_2), 3.13 (dd, 1H, J = 5.5, 5.5 Hz, Bn-Ha), 2.91 (dd, 1H, J = 8.2, 8.3 Hz, Bn-Hb), 2.41 (s, 3H, acetyl CH_3), 1.22 (t, 3H, J = 7.1 Hz, ester CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 194.7, 174.8, 170.7, 154.6, 162.3, 151.4, 141.6, 139.4, 128.4, 127.5, 114.6, 55.2, 53.6, 44.4, 36.6, 25.7 ppm; EIMS: *m*/*z* (%) = 477 (M^+, 27), 404 (8), 285 (58), 257 (62), 233 (29), 176 (52), 148 (67), 124 (53), 104 (61), 91 (100), 82 (67), 65 (54), 43 (58).

Ethyl 1-[2-(5-acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-1-oxoethyl]pyrrolidine-2-carboxylate (**11b**, $C_{22}H_{25}N_3O_6$)

Method A: yield 84%; method B: 6 h reflux, yield 63%; m.p.: 33–35 °C; IR (KBr): $\bar{\nu}$ = 3,263, 1,726, 1,687, 1,652, 1,612, 1,595, 1,542 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 10.48 (bs, 1H, NH), 8.71 (s, 1H, C_6H), 7.36 (m, 5H, Ar–H), 5.02 (s, 2H, N–CH_2), 4.81 (s, 2H, N–CH_2), 4.29 (dd, 1H, J = 8.4, 8.0 Hz, CH), 4.21 (q, 2H, J = 7.1 Hz, ester O–CH_2), 3.11 (m, 2H, ring CH_2), 2.42 (m, 5H, ring CH_2, acetyl CH_3), 2.10 (m, 2H, ring CH_2), 1.29 (t, 3H, J = 7.1 Hz, ester CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.7, 171.5, 167.7, 162.3, 154.6, 151.4, 136.4, 128.4, 126.5, 114.6, 65.7, 61.2, 53.9, 49.6, 46.9, 28.9, 24.7, 14.1 ppm; EIMS: *m*/*z* (%) = 427 (M^+, 14), 285 (54), 257 (12), 142 (38), 124 (42), 91 (100), 43 (36).

Ethyl 2-[[2-(5-acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-1-oxoethyl]amino]-3-(4-hydroxyphenyl)propionate (**11c**, $C_{26}H_{27}N_3O_7$)

Method A: yield 88%; method B: 8 h reflux, yield 60%; m.p.: 43–45 °C; IR (KBr): $\bar{\nu}$ = 3,263, 1,746, 1,685, 1,667, 1,632, 1,602, 1,538 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 10.56 (bs, 1H, NH), 8.61 (s, 1H, C_6H), 7.13 (m, 7H, Ar–H), 7.35 (d, 2H, Ar–H), 5.02 (s, 2H, N–CH_2), 4.82 (s, 2H, N–CH_2), 4.74 (dd, 1H, J = 8.4, 8.0 Hz, CH), 4.27 (q, 2H, J = 7.0 Hz, ester O–CH_2), 3.23 (dd, 1H, J = 5.5, 5.5 Hz, Bn–Ha), 2.85 (dd, 1H, J = 8.2, 8.3 Hz, Bn–Hb), 2.4 (s, 3H, acetyl CH_3), 1.25 (t, 3H, J = 7.0 Hz, ester CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 194.4, 174.3, 170.8, 162.2, 154.9, 151.5, 141.1, 139.7, 128.8, 127.4, 114.2, 55.1, 53.4, 44.5, 36.4, 25.5 ppm; EIMS: *m*/*z* (%) = 517 (M^+, 8), 479 (22), 373 (22), 341 (9), 317 (11), 302 (28), 277 (36), 245 (39), 234 (7), 219 (9), 124 (23), 91 (100), 77 (25), 43 (31).

Ethyl 2-[[2-(5-acetyl-3-benzyl-3,4-dihydro-2,4-dioxopyrimidin-1(2H)-yl)-1-oxoethyl]amino]pentanoate (**11d**, $C_{22}H_{27}N_3O_6$)

Method A: yield 78%; method B: 7 h reflux, yield 65%; m.p.: 63–65 °C; IR (KBr): $\bar{\nu}$ = 3,258, 1,729, 1,685, 1,654, 1,624, 1,615, 1,541 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 10.52 (bs, 1H, NH), 8.70 (s, 1H, C_6H), 7.26 (m, 5H, Ar–H), 5.18 (s, 2H, N–CH_2), 4.78 (s, 2H, N–CH_2), 4.51 (dd, 1H, J = 8.4, 8.0 Hz, CH), 4.21 (q, 2H, J = 7.1 Hz, ester O–CH_2), 2.42 (s, 3H, acetyl CH_3), 1.90 (q, 2H, J = 5.4 Hz, CH_2), 1.33 (m, 2H, CH_2), 1.29 (t, 3H, J = 7.1 Hz, ester CH_3), 0.90 (t, 3H, J = 5.4 Hz, CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 193.7, 171.5, 170.7, 162.3, 154.6, 151.4, 136.4, 126.7, 114.6, 61.3, 56.1, 55.9, 46.9, 28.9, 18.8, 14.1, 13.8 ppm; EIMS: *m*/*z* (%) = 429 ($M^{+\cdot}$ 9) 285 (22), 257 (5), 144 (2), 91 (100), 65 (9), 43 (9).

Acknowledgments The authors gratefully acknowledge financial support of this project by UGC, New Delhi, India. Also we thanks Principal, K.T.H.M. College, Nashik, 422 002 for facilities.

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