One-pot synthesis of α-acyloxycarboxamidobarbiturates from alloxans, carboxylic acids, and isocyanides

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A simple, efficient, and high yielding one-pot protocol for the synthesis of novel highly substituted α-acyloxycarboxamidobarbiturates has been developed by a three-component reaction of alloxans, various carboxylic acids, and alkyl or aryl isocyanides in acetonitrile at room temperature.

Keywords: alloxan, carboxylic acid, isocyanide, multicomponent reaction, Passerine reaction

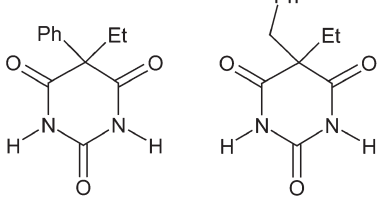
The barbiturates, therapeutically used as sedatives, hypnotics, anaesthetics and anticonvulsants, are a class of drugs derived from barbituric acid, a synthetic condensation product of malonic acid and urea. They differ mainly in the substitution pattern at the C-5 position with some also including an *N*-methyl at N-1.[1]

Reportedly, in the course of the last century over 2,500 barbiturates have been synthesised with more than 50 of these presently marketed for clinical use throughout the world.[2] Their use was widespread and many still have some use today. One hundred years after the introduction in clinical pharmacology of the original compound, oxybarbiturates, in general, continue to be the selected drugs in the treatment of some serious forms of insomnia and in some types of epilepsy.[3] Furthermore, barbiturates are frequently used for the treatment of intracranial hypertension after severe head injury.[4] Under these conditions, they can decrease cerebral metabolic demands, oxygen need and intracranial pressure.[5]

The structure and conformation of the C-5 side chains of the barbiturates have been suggested to be determinants of the different biological activities. For instance, slight structural modifications in many depressant barbiturates such as phenobarbital, the most widely used anticonvulsant worldwide and the oldest still in use, produce compounds with excitatory or convulsant activity, *e.g.*, 5-benzyl-5-ethylbarbituric acid,[6–9] a homologue of phenobarbital (Scheme 1).

The peptide bond is an important functional group in organic chemistry, biochemistry and medicine.[10–12] Peptides play crucial roles in the human body and other organisms.[13–15] Due to the biological significance of molecules with the barbiturate moiety we have combined amides and barbiturates as molecular entities through carbon–carbon bond formation in order to create new molecules. Considering the versatile activities of these structures, we think it would be of interest to combine the barbiturate moiety and the peptide bond in view of their promising applications in medicinal chemistry and biological investigations.

The peptide bond is traditionally synthesised by the reaction of an amine with an activated carboxylic acid.[16–19] Among the



I Phenobarbital

II 5-Benzyl-5-methylbarbituric acid

Scheme 1

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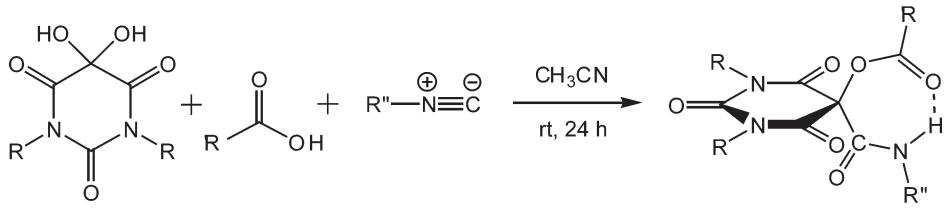
protocols for the synthesis of peptide bond, one of the important methods is the Passerini three-component reaction (P-3CR).[20] The most commonly used P-3CR, is one in which a carboxylic acid, an oxo compound and an isocyanide are reacted to result in α-acyloxycarboxamide products. This group of compounds is present in the structures of many natural products, such as the pharmacologically active depsipeptides.[21,22] Also the P-3CR reaction can lead to interesting and potentially bioactive peptidomimetic compounds and offers an inexpensive and rapid way to generate compound libraries.[23,24]

Alloxan (pyrimidine-2,4,5,6(1*H*,3*H*)-tetrone) and its derivatives are very interesting vicinal tricarbonyl compounds, which have four electrophilic C=O sites.[25] Our literature survey at this stage revealed that, there is no report yet available on the use of alloxan derivatives in the Passerini reaction. In the present study, the formation of poly-functional α-acyloxycarboxamidobarbiturates by a three-component condensation reaction of isocyanides is reported.

The one-pot three-component condensation reactions of alloxan derivatives **1** with various carboxylic acids **2** in the presence of alkyl or aryl isocyanides **3** proceeded at room temperature in acetonitrile and were complete after 24 h to afford the corresponding α-acyloxycarboxamidobarbiturates **4** in good yields (Scheme 2). ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of α-acyloxycarboxamidobarbiturates **4**. No other products could be detected by NMR spectroscopy. Compounds **4a–m** are stable white solids, whose structures were established by IR, ^{1}H, ^{13}C NMR spectroscopy and elemental analysis. The full results are summarised in Table 1.

To survey the generality and scope of this one-pot three-component protocol, the methodology was applied to the synthesis of a variety of 5-[(alkyl or arylamino)carbonyl]-2,4,6-trioxohexahydropyrimidin-5-yl carboxylate derivatives **4a–m**. With the optimal conditions in hand, we extended the reaction to other carboxylic acids and the results are indicated in Table 1. Seven derivatives of carboxylic acids including aromatic, aliphatic and α,β-unsaturated carboxylic acids, afforded α-acyloxycarboxamidobarbiturates in from good to excellent isolated yields. To explore the scope of this reaction with respect to reactive isocyanides, we have examined seven alkyl or aryl isocyanides. We have found that the reaction proceeds very efficiently with both sterically hindered and less hindered alkyl or aryl isocyanides.

The central carbonyl group in vicinal tricarbonyl compounds is a strongly electrophilic entity, accounting for the fact that tricarbonyls are hydrated at this site.[26] In solution, the alloxan hydrate is in equilibrium with the parent tricarbonyl, and in this form, they undergo reactions with a broad range of nucleophiles. A probable mechanistic rationale portraying a sequence of events for this three-component coupling is postulated in Scheme 3. The first step is believed to be the formation of a loosely hydrogen-bonded adduct **5** from the alloxan derivative and the carboxylic acid followed by α-addition of the electrophilic carbonyl carbon and the nucleophilic oxygen atom of



1 2 3 4

Scheme 2

Table 1 Structure of compounds **4a–m**

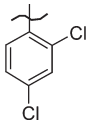
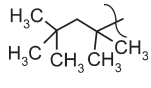
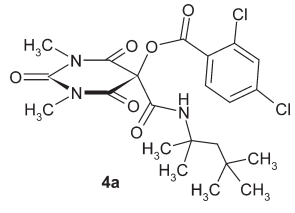
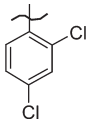
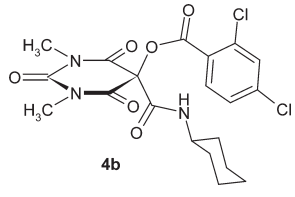
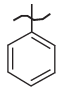
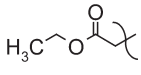
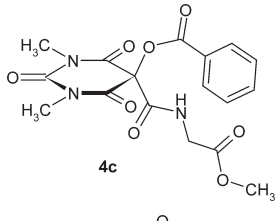
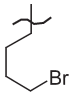
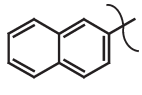
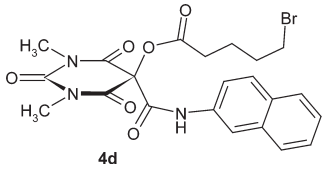
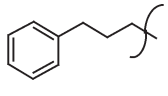
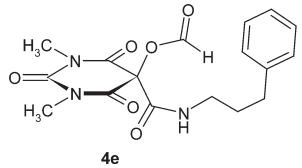
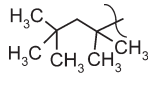
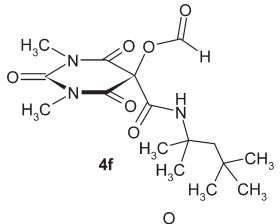
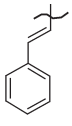
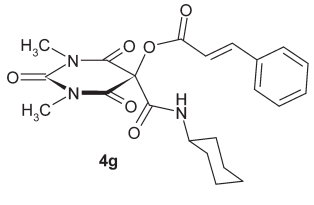
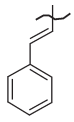
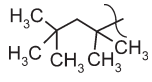
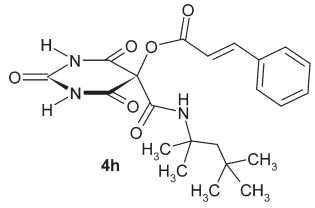
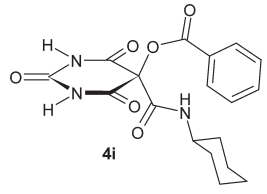
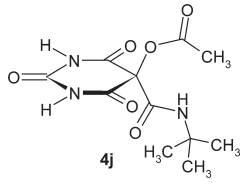
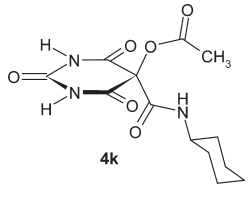
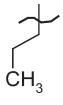
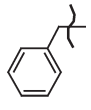
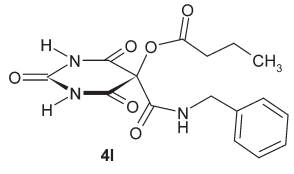
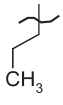
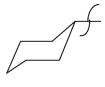
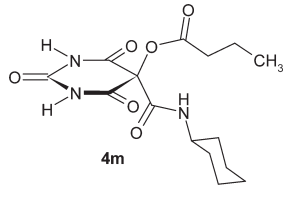
Entry	R	R′	R″	Product	Yield/%[a]
1	CH_3			 **4a**	83
2	CH_3			 **4b**	85
3	CH_3			 **4c**	79
4	CH_3			 **4d**	91
5	CH_3	H		 **4e**	78
6	CH_3	H		 **4f**	86
7	CH_3			 **4g**	90

Table 1 *Continued*

Entry	R	R′	R″	Product	Yield/%[a]
8	H			 **4h**	92
9	H			 **4i**	88
10	H	CH_3		 **4j**	79
11	H	CH_3		 **4k**	76
12	H			 **4l**	78
13	H			 **4m**	80

[a]Purified yield, which is >95% as determined by ^{1}H NMR spectroscopy.

the carboxylic acid to the isocyanide carbon atom with formation of a **6** via cyclic transition state comprising all three parent compounds. The α-adduct which cannot be isolated rearranges in an intramolecular transacylation to the stable α-acyloxycarboxamidobarbiturate **4**.

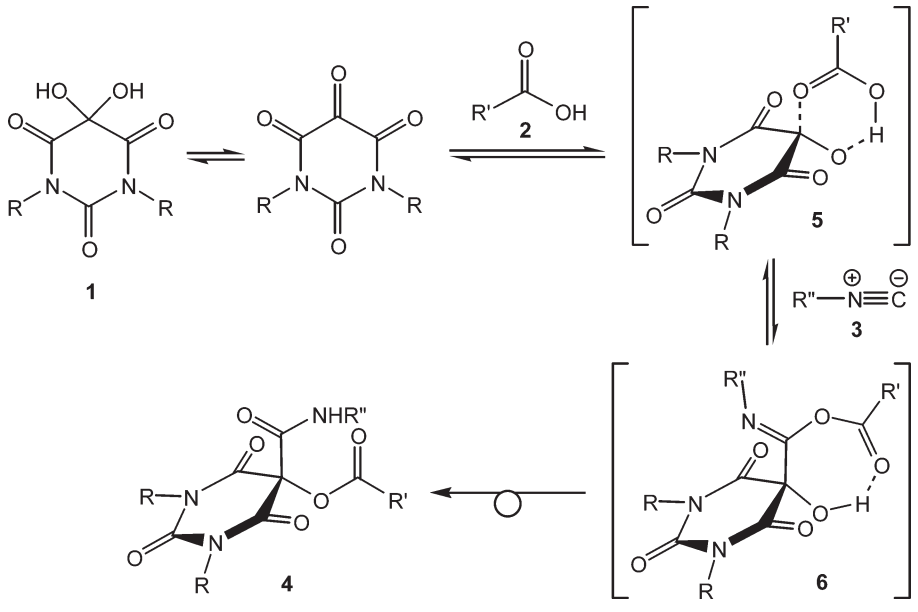
In summary, alloxan was introduced for the first time as a novel oxo component in a Passerini reaction. Several carboxylic acids and alkyl or aryl isocyanides were able under these reaction conditions to afford diverse α-acyloxycarboxamidobarbiturates of potential synthetic and pharmaceutical interest in good to excellent yields. The present method carries the advantage of being performed under neutral conditions and requires no activation or modification of the reactants.

Experimental

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using an Elementar Vario EL *III* instrument. FT-IR Spectra were recorded on a Bruker Equinox-55 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 400.13 and 100.77 MHz, respectively, with $CDCl_3$, CD_3SOCD_3 or CD_3COCD_3 as solvents and calibrated using the residual undeuterated solvent as an internal reference. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal reference. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualised with UV light. All chemical reagents were obtained from Merck, Fluka, Acros or Aldrich and were used without further purification.

Synthesis of **4a–m***; typical procedure*

To a magnetically stirred solution of 1,3-dimethylaloxan (0.189 g, 1.0 mmol) and 2,4-dichlorobenzoic acid (0.191 g, 1.0 mmol) in CH_3CN (10 cm^3) was added 1,1,3,3-tetramethlbutyl isocyanide (0.140 g, 1.0 mmol) at room temperature (25 °C). The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure and the viscous residue was purified by column chromatography (Merck 230–400 mesh) using *n*-hexane-EtOAc (4:1) as eluent to give **4a** as a white powder (0.415 g, 83%). The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.



Scheme 3

1,3-Dimethyl-2,4,6-trioxo-5-{[(1,1,3,3-tetramethylbutyl)amino]carbonyl} hexahydropyrimidin-5-yl 2,4-dichlorobenzoate (**4a**): M.p. 143–145 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3409 (N–H), 1693, 1665, 1629 (C=O); ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 0.94 (9 H, s, CMe_3), 1.38 (6 H, s, CMe_2), 1.69 (2 H, s, CH_2), 3.34 (6 H, s, 2 NCH_3), 6.74 (1 H, s, NH), 7.34–7.87 (3 H, m, arom.); ^{13}C NMR ($CDCl_3$, 100.7 MHz): 162.7, 162.5, 158.3, 150.6, 140.5, 135.1, 134.0, 131.5, 127.7, 125.3, 80.6, 57.0, 51.3, 31.5, 31.3, 29.4, 28.8; Anal. Calcd for $C_{22}H_{27}Cl_2N_3O_6$ (500.37): C, 52.81; H, 5.44; N, 8.40%. Found: C, 52.72; H, 5.42; N, 8.43%.

5-[(Cyclohexylamino)carbonyl]-1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl 2,4-dichlorobenzoate (**4b**): White powder (0.400 g, 85%); m.p. 106–108 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3337 (N–H), 1700, 1672, 1609 (C=O); ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.18–1.93 (10 H, m, 5 CH_2), 3.37 (6 H, s, 2 NCH_3), 3.68–3.74 (1 H, m, NHC*H*), 6.81 (1 H, d, $^3J_{HH}$ = 6.3 Hz, NH), 7.38–7.91 (3 H, m, arom.); ^{13}C NMR ($CDCl_3$, 100.7 MHz): 162.9, 162.7, 159.2, 150.7, 140.8, 135.3, 134.3, 131.7, 127.9, 125.4, 80.6, 49.8, 32.6, 29.7, 25.4, 24.6; Anal. Calcd for $C_{20}H_{21}Cl_2N_3O_6$ (470.30): C, 51.08; H, 4.50; N, 8.93. Found: C, 51.26; H, 4.51; N, 8.95%.

Methyl N-{[5-(benzoyloxy)-1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl]carbonyl}glycinate (**4c**): White powder (0.309 g, 79%); m.p. 140–142 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3354 (N–H), 1749, 1705, 1669 (C=O); ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 3.36 (3 H, s, OCH_3), 3.79 (2 H, s, CH_2), 4.07 (1 H, t, $^3J_{HH}$ = 4.6 Hz, N*H*CH_2), 7.42–8.08 (5 H, m, arom.); ^{13}C NMR ($CDCl_3$, 100.7 MHz): 169.0, 164.5, 163.0, 160.8, 150.6, 135.0, 130.5, 129.1, 127.0, 79.6, 53.1, 41.8, 30.1; Anal. Calcd for $C_{17}H_{17}N_3O_8$ (391.33): C, 52.18; H, 4.38; N, 10.74. Found: C, 52.30; H, 4.40; N, 10.70%.

1,3-Dimethyl-5-[(2-naphthylamino)carbonyl]-2,4,6-trioxohexahydropyrimidin-5-yl 5-bromopentanoate (**4d**): White powder (0.459 g, 91%); m.p. 86–88 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3475 (N–H), 1683, 1610 (C=O); ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.86–1.96 (4 H, m, $BrCH_2CH_2CH_2CH_2C$=O), 2.67 (2 H, t, $^3J_{HH}$ = 7.1 Hz, $BrCH_2CH_2CH_2CH_2C$=O), 3.35–3.44 (8 H, m, 2 NCH_3 + $BrCH_2CH_2CH_2CH_2C$=O), 7.42–7.48 and 7.74–7.80 (6 H, 2 m, arom.), 8.14 (1 H, s, arom.), 8.49 (1 H, s, NH); ^{13}C NMR ($CDCl_3$, 100.7 MHz): 171.0, 163.2, 158.5, 150.6, 133.6, 133.1, 131.5, 129.3, 128.0, 127.8, 127.1, 126.1, 119.8, 118.1, 79.7, 33.1, 32.5, 31.5, 29.9, 29.8, 23.2; Anal. Calcdfor $C_{22}H_{22}BrN_3O_6$ (504.33): C, 52.39; H, 4.40; N, 8.33. Found: C, 52.50; H, 4.44; N, 8.35%.

1,3-Dimethyl-2,4,6-trioxo-5-{[(3-phenylpropyl)amino]carbonyl} hexahydropyrimidin-5-yl formate (**4e**): White powder (0.282 g, 78%); m.p. 110–112 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3460 (N–H), 1727, 1706, 1666 (C=O). ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.87 (2 H, qu, $^3J_{HH}$ = 7.1 Hz, $NHCH_2CH_2CH_2Ph$), 2.63 (2 H, t, $^3J_{HH}$ = 7.1 Hz, $NHCH_2CH_2CH_2Ph$), 3.29–3.34 (8 H, m, $NHCH_2CH_2CH_2Ph$ + 2 NCH_3), 6.70 (1 H, br s, NH), 7.14–7.29 (5 H, m, arom.), 8.05 (1 H, s, O=CH); ^{13}C NMR ($CDCl_3$, 100.7 MHz): 162.5, 159.9, 157.6, 150.50, 140.9, 128.8, 128.5, 126.4, 79.2, 40.1, 33.2, 30.6, 29.7; Anal. Calcd for $C_{17}H_{19}N_3O_6$ (361.34): C, 56.51; H, 5.30; N, 11.63. Found: C, 56.63; H, 5.34; N, 11.65%.

1,3-Dimethyl-2,4,6-trioxo-5-{[(1,1,3,3-tetramethylbutyl)amino]carbonyl}hexahydropyrimidin-5-yl formate (**4f**): White powder (0.306 g, 86%); m.p. 133–135 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3306 (N–H), 1747, 1695, 1658 (C=O); ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 0.97 (9 H, s, CMe_3), 1.39 (6 H, s, CMe_2), 1.68 (2 H, s, CH_2), 3.33 (6 H, s, 2 NCH_3), 6.50 (1 H, br s, NH), 8.07 (1 H, s, O=CH); ^{13}C NMR ($CDCl_3$, 100.7 MHz): 162.7, 158.2, 157.5, 150.6, 79.4, 57.1, 52.0, 31.7, 31.5, 29.7, 28.8; Anal. Calcd for $C_{16}H_{25}N_3O_6$ (355.38): C, 54.07; H, 7.09; N, 11.82. Found: C, 53.94; H, 7.06; N, 11.79%.

5-[(Cyclohexylamino)carbonyl]-1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl (2E)-3-phenylacrylate (**4g**): White powder (0.385 g, 90%); m.p. 193–195 °C (dec.); IR (KBr) ($\nu_{max,}$ cm^{-1}): 3260 (N–H), 1744, 1712, 1661 (C=O); ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ_H 1.24–1.95 (10 H, m, 5 CH_2), 3.36 (6 H, s, 2 NCH_3), 3.68–3.72 (1 H, m, NHC*H*), 6.58 (1 H, d, $^3J_{HH}$ = 7.7 Hz, NH), 6.64 and 7.77 (2 H, d, $^3J_{HH}$ = 16.0 Hz, C*H*=C*H*-Ph), 7.38–7.56 (5 H, m, arom.); ^{13}C NMR ($CDCl_3$, 100.7 MHz): 164.7, 163.6, 159.7, 150.8, 149.8, 133.6, 131.7, 129.3, 128.8, 114.4, 49.9, 32.7, 29.6, 25.5, 24.9; Anal. Calcd for $C_{22}H_{25}N_3O_6$ (427.45): C, 61.82; H, 5.90; N, 9.83. Found: C, 61.97; H, 5.91; N, 9.87%.

2,4,6-Trioxo-5-{[(1,1,3,3-tetramethylbutyl)amino]carbonyl} hexahydropyrimidin-5-yl (2E)-3-phenylacrylate (**4h**): White powder (0.396 g, 92%); m.p. 200–202 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3335 (O-H), 3300, 3240, 3115 (N–H), 1768, 1704, 1646 (C=O); ^{1}H NMR (DMSO-d_6, 400.1 MHz): δ_H 0.93 (9 H, s, CMe_3), 1.35 (6 H, s, CMe_2), 1.70 (2 H, s, CH_2), 6.95 and 7.85 (2 H, d, $^3J_{HH}$ = 16.0 Hz, C*H*=C*H*-Ph), 7.46–7.48 and 7.73–7.74 (6 H, 2 m, arom. + NH), 11.97 (2 H, s, N*H*CON*H*); ^{13}C NMR (DMSO-d_6, 100.7 MHz): 164.7, 159.8, 150.5, 149.1, 134.1, 132.1, 129.6, 129.1, 116.4, 79.5, 56.6, 50.8, 31.9, 31.7, 29.4; Anal. Calcd for $C_{22}H_{27}N_3O_6$ (429.46): C, 61.53; H, 6.34; N, 9.78. Found: C, 61.68; H, 6.31; N, 9.81%.

5-[(Cyclohexylamino)carbonyl]-2,4,6-trioxohexahydropyrimidin-5-yl benzoate (**4i**): White powder (0.329 g, 88%); m.p. 180–182 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3277, 3113 (N–H), 1769, 1703, 1670 (C=O); ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 400.1 MHz): δ_H 0.77–1.84 (10 H, m, 5 CH_2), 3.48–3.60 (1 H, m, NHC*H*), 7.35–8.14 (6 H, 3 m, arom. + NH), 11.82 (2 H, s, N*H*CON*H*); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 100.7 MHz): 164.7, 160.1, 150.1, 134.8, 130.8, 128.8, 127.1, 79.6, 49.8, 32.0, 25.3, 25.2; Anal. Calcd for $C_{18}H_{19}N_3O_6$ (373.36): C, 57.90; H, 5.13; N, 11.25. Found: C, 58.03; H, 5.09; N, 11.31%.

5-[(tert-Butylamino)carbonyl]-2,4,6-trioxohexahydropyrimidin-5-yl acetate (**4j**): White powder (0.226 g, 79%); m.p. 149–151 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3354, 3249 (N–H), 1770, 1714, 1670 (C=O); ^{1}H NMR (Acetone-d_6, 400.1 MHz): δ_H 1.33 (9 H, s, $C(CH_3)_3$), 2.21 (3 H, s, CH_3), 7.61 (1 H, br s, NH), 10.76 (2 H, br s, N*H*CON*H*); ^{13}C NMR (Acetone-d_6, 100.7 MHz): 168.9, 164.0, 159.9, 149.0, 79.2, 52.3, 27.5, 18.9; Anal. Calcd for $C_{11}H_{15}N_3O_6$ (285.25): C, 46.32; H, 5.30; N, 14.73. Found: 46.19; H, 5.28; N, 14.70%.

5-[(Cyclohexylamino)carbonyl]-2,4,6-trioxohexahydropyrimidin-5-yl acetate (**4k**): White powder (0.237 g, 76%); m.p. 208–210 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3400, 3225, 3110 (N–H), 1766, 1729, 1667 (C=O); ^{1}H NMR (Acetone-d_6, 400.1 MHz): δ_H 1.12–2.18 (10 H, m, 5 CH_2), 2.88 (3 H, s, CH_3), 3.63–3.68 (1 H, m, NHC*H*), 7.84 (1 H, br s, NH), 10.71 (2 H, br s, N*H*CON*H*); ^{13}C NMR (Acetone-d_6, 100.7 MHz): 169.0, 164.0, 159.8, 148.9, 79.1, 49.4, 31.9, 25.2, 24.9, 18.9; Anal. Calcd for $C_{13}H_{17}N_3O_6$ (311.29): C, 50.16; H, 5.50; N, 13.50. Found: C, 50.27; H, 5.48; N, 13.46%.

5-[(Benzylamino)carbonyl]-2,4,6-trioxohexahydropyrimidin-5-yl butyrate (**4l**): White powder (0.271 g, 78%); m.p. 166–168 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3335, 3308, 3294 (N–H), 1719, 1701, 1678 (C=O); ^{1}H NMR (DMSO-d_6, 400.1 MHz): δ_H 0.87 (3 H, t, $^3J_{HH}$ = 7.4 Hz, $CH_2CH_2CH_3$), 1.57 (2 H, sex., $^3J_{HH}$ = 7.4 Hz, $CH_2CH_2CH_3$), 2.52 (2 H, t, $^3J_{HH}$ = 7.4 Hz, $CH_2CH_2CH_3$), 4.30 (2 H, d, $^3J_{HH}$ = 6.1 Hz, NHCH_2), 7.14–7.30 (5 H, m, arom.), 9.30 (1 H, t, $^3J_{HH}$ = 6.1 Hz, NH), 12.10 (2 H, br s, N*H*CON*H*); ^{13}C NMR (DMSO-d_6, 100.7 MHz): 172.5, 165.0, 161.4, 150.4, 138.8, 129.0, 127.7, 127.5, 79.1, 43.1, 34.8, 18.4, 13.7; Anal. Calcd for $C_{16}H_{17}N_3O_6$ (347.32): C, 55.33; H, 4.93; N, 12.10. Found: C, 55.51; H, 4.90; N, 12.11%.

5-[(Cyclohexylamino)carbonyl]-2,4,6-trioxohexahydropyrimidin-5-yl butyrate (**4m**): White powder (0.272 g, 80%); m.p. 179–181 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3265, 3100 (N–H), 1728, 1705, 1630 (C=O); ^{1}H NMR (DMSO-d_6, 400.1 MHz): δ_H 0.84 (3 H, t, $^3J_{HH}$ = 7.4 Hz, $CH_2CH_2CH_3$), 1.02–1.67 (12 H, m, 5 CH_2 + $CH_2CH_2CH_3$), 2.54 (2 H, t, $^3J_{HH}$ = 7.4 Hz, $CH_2CH_2CH_3$), 8.36 (1 H, d, $^3J_{HH}$ = 8.3 Hz, NH), 11.95 (2 H, br s, N*H*CON*H*); ^{13}C NMR (DMSO-d_6, 100.7 MHz): 172.6, 165.1, 160.3, 150.4, 79.1, 49.8, 34.7, 32.3, 25.6, 25.4, 18.3, 13.7; Anal. Calcd for $C_{15}H_{21}N_3O_6$ (339.34): C, 53.09; H, 6.24; N, 12.38. Found: C, 53.29; H, 6.21; N, 12.41%.

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References

1 J.W. Dundee and P.D.A. McIlroy, *Anaesthesia*, 1982, **37**, 726.
2 F. López-Munoz, R. Ucha-Udabe and C. Alamo, *Neuropsychiatr. Dis. Treat.*, 2005, **1**, 329.
3 D.S. Charney, S.J. Mihic and Harris, R.A., eds J.G. Hardman and L.E. Limbird, *Goodman & Gilman's The pharmacological basis of therapeutics.* 2001,10th edn. McGraw Hill, New York, pp. 399–427.
4 J.E. Wilberger and D. Cantella, *New Horiz.*, 1995, **3**, 469.
5 I. Roberts, *Cochrane Database Syst. Rev.*, 2000, **2**, CD000033.
6 S.B. King, E.S. Stratford, C.R. Craig and E.K. Fifer, *Pharmaceut. Res.*, 1995, **12**, 1240.
7 J.A. Vida and E.H. Gerry, *Anticonvulsants-medicinal chemistry. A series of monographs*, eds J.A. Vida, Vol. 15, Academic Press, New York, 1977, pp. 151–173.
8 P.R. Andrews, G.P. Jones and D. Lodge, *Eur. J. Pharmacol.*, 1979, **55**, 115.
9 P.R. Andrews, G.P. Jones and D.B. Poulton, *Eur. J. Pharmacol.*, 1982, **79**, 61.
10 T. Cupido, J. Tulla-Puche, J. Spengler and F. Albericio, *Curr. Opin. Drug Discov. Devel.*, 2007, **10**, 768.
11 J.W. Bode, *Curr. Opin. Drug Disco. Devel.*, 2006, **9**, 765.
12 J.M. Humphrey and A.R. Chamberlin, *Chem. Rev*, 1997, **97**, 2243.
13 F.-F. Tian, P. Zhou and Z.-L. Li, *J. Mol. Struct.*, 2007, **830**, 106.
14 M. Shu, H. Mei, S. Yang, L. Liao and Z. Li, *QSAR Comb. Sci.*, 2009, **28**, 27.
15 T. Day and S.A. Greenfield, *Exp. Brain Res.*, 2004, **155**, 500.
16 R.C. Larock, *Comprehensive organic transformations*; VCH, New York, 1999.
17 E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606.
18 S.Y. Han and Y.A. Kim, *Tetrahedron*, 2004, **60**, 2447.
19 C.A.G.N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827.
20 L. Banfi and R. Riva, *Org. React.* 2005, **65**, 1.
21 A. Dömling, *Chem. Rev.*, 2006, **106**, 17.
22 A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, 2000, **39**, 3168.
23 I. Ugi and S. Heck, *Comb. Chem. High T. Scr.*, 2001, **4**, 1.
24 A. Ulaczyk-Lesanko and D.G. Hall, *Curr. Opin. Chem. Biol.*, 2005, **9**, 266.
25 D.B. Hansen and M.M. Joullié, *Chem. Soc. Rev.*, 2005, **34**, 408.
26 M.B. Rubin and R. Gleiter, *Chem. Rev.*, 2000, **100**, 1121.