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# Novel multicomponent reactions of primary amines and alkyl propiolates with alloxan derivatives in water

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ABSTRACT

A water-accelerated multicomponent synthesis of organic target molecules has been used as a key method for the preparation of novel barbiturate derivatives. The three-component condensation reactions of primary amines with alkyl propiolates in the presence of alloxan derivatives in water are developed as efficient and clean green synthetic procedures for the high-yielding preparation of alkyl 2-(5-hydroxy-2,4,6-trioxohexahydro-5-pyrimidinyl)-3-(alkyl or arylamino)-2-propenoates. The above synthetic protocol provides rapid access to novel and diversely substituted barbiturate derivatives.



## 1. Introduction

Barbiturates have attracted the attention of pharmaceutical community for more than a century due to their therapeutic value.[1] Barbiturate derivatives are widely used as sedative hypnotic drugs under a variety of conditions and are also employed for anaesthesia.[2] For example, barbiturates like phenobarbital (Luminal) **1** and pentobarbital (Nembutal) **2** were long used as anxiolytics and hypnotics (Fig. 1). Moreover, phenobarbital is the most widely used anticonvulsant worldwide and the oldest still in use. Slight structural modifications in many depressant barbiturates produce compounds with excitatory or convulsant activity, e.g., 5-benzyl-5-ethylbarbituric acid **3**, a homologue of phenobarbital. The structure and conformation of the C-5 side chains of the barbiturates have been suggested to be determinants of the different biological activities. Many 5,5-disubstituted barbituric acid derivatives have been synthesized in an effort to develop a structure–activity relationship for these compounds. For instance, Ro 28-2653 **4**[3] belongs to a new barbiturate class of matrix metalloproteinase (MMP) inhibitors with high selectivity for the gelatinases A and B (MMP-2 and MMP-9), which have been implicated in tumour growth and metastasis.[3,4] Preclinically, Ro 28-2653 has been shown to reduce tumour growth and extend survival time of tumour-bearing animals[5] and, more recently, to induce apoptosis in the tumour cells.[6,7]

One of the powerful tools used to combine economic aspects with the environmental concerns is performing organic reactions in water; this strategy consists of two or more synthetic steps, which are carried out in water as a cheap, nontoxic, environmentally friendly solvent, in a one-step reaction, without isolation of any intermediate thus reducing time, saving money, energy and raw materials.[8] Although, production of a contaminated aqueous waste stream can have significant economic impacts, for example, concentration of contaminated water streams by distillation is very energy intensive compared to say concentration of propanol waste stream.[9] However, the development and implementation of processes using water as solvent may serve as one avenue for lowering

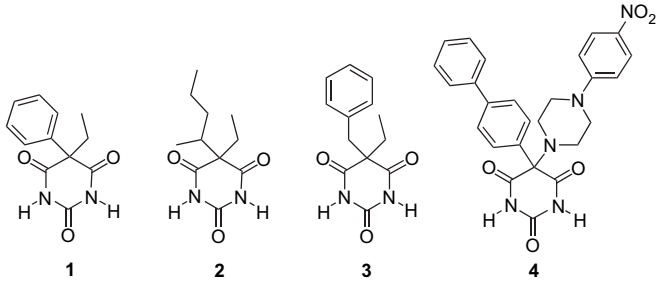


**Figure 1.** Selected examples of biologically active barbiturates.

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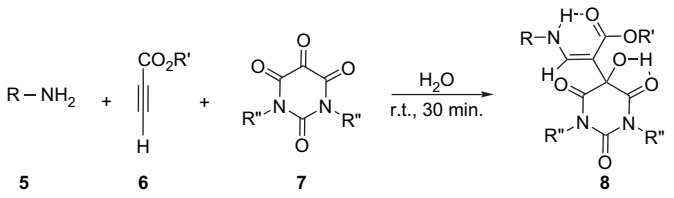
**Table 1**
Three-component condensation reactions of primary amines, alkyl propiolates and alloxan derivatives




5 6 7 8

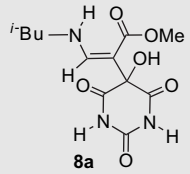
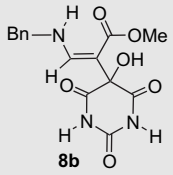
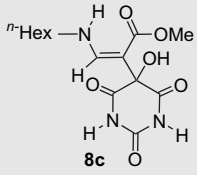
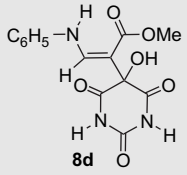
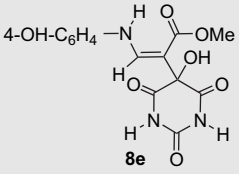
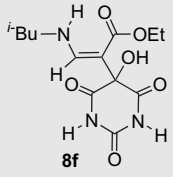
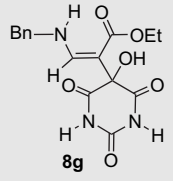
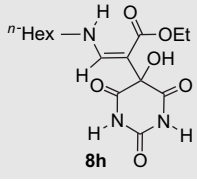
| Entry | R | R′ | R″ | Product | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | *iso*-Butyl | Methyl | H |  **8a** | 82 |
| 2 | Benzyl | Methyl | H |  **8b** | 85 |
| 3 | *n*-Hexyl | Methyl | H |  **8c** | 91 |
| 4 | Phenyl | Methyl | H |  **8d** | 77 |
| 5 | 4-Hydroxyphenyl | Methyl | H |  **8e** | 84 |
| 6 | *iso*-Butyl | Ethyl | H |  **8f** | 79 |
| 7 | Benzyl | Ethyl | H |  **8g** | 93 |
| 8 | *n*-Hexyl | Ethyl | H |  **8h** | 90 |

**Table 1** (*continued*)

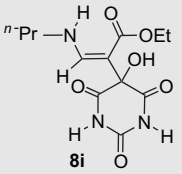
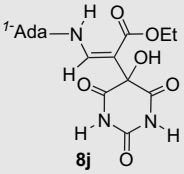
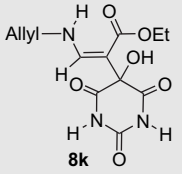
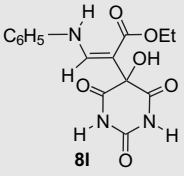
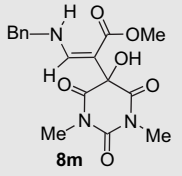
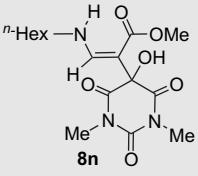
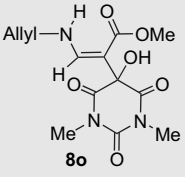
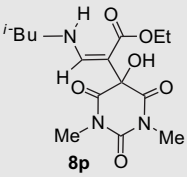
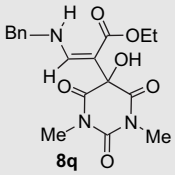
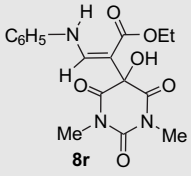
| Entry | R | R′ | R″ | Product | Yield[a] (%) |
|---|---|---|---|---|---|
| 9 | *n*-Propyl | Ethyl | H |  **8i** | 88 |
| 10 | 1-Adamantyl | Ethyl | H |  **8j** | 81 |
| 11 | Allyl | Ethyl | H |  **8k** | 95 |
| 12 | Phenyl | Ethyl | H |  **8l** | 76 |
| 13 | Benzyl | Methyl | Methyl |  **8m** | 80 |
| 14 | *n*-Hexyl | Methyl | Methyl |  **8n** | 89 |
| 15 | Allyl | Methyl | Methyl |  **8o** | 90 |
| 16 | *iso*-Butyl | Ethyl | Methyl |  **8p** | 75 |

**Table 1** (*continued*)

| Entry | R | R′ | R″ | Product | Yield[a] (%) |
|---|---|---|---|---|---|
| 17 | Benzyl | Ethyl | Methyl |  **8q** | 84 |
| 18 | Phenyl | Ethyl | Methyl |  **8r** | 72 |

[a] Refers to purified yield. Compound purity is >95% as determined by $^1$H NMR.

both the environmental impact of the chemical industry and the hundred billion dollar costs associated with environmental regulation compliance.[10] Moreover, multicomponent condensation reactions due to their productivity, simple procedures, convergence and facile execution are one of the important strategies in combinatorial chemistry.[11] Therefore, the discovery and development of novel multicomponent reactions have attracted great attention from research groups working in various areas such as drug discovery, organic synthesis and material science. As a result, one-pot multicomponent reactions in organic chemistry have expanded rapidly.[12]

Continuing our efforts directed towards the straightforward preparation of biologically active target molecules through multicomponent reactions,[13] we performed the synthesis of some novel barbiturates via a three-component reaction of primary amines, alkyl propiolates and alloxan derivatives at room temperature by employing water as the reaction medium. In fact, as clearly stated by Sheldon, it is generally recognized that "the best solvent is no solvent and if a solvent (diluent) is needed then water is prefered".[14] The use of water as a reaction medium represents remarkable benefits since this green solvent is highly polar and therefore immiscible with most organic compounds; moreover, the water-soluble by-products reside and separation of the organic materials is thus easy. A further advantage is that many organic reactions exhibit rate enhancement in water.[15]

## 2. Results and discussion

In the present investigation, a mixture of primary amine **5**, alkyl propiolate **6** and alloxan derivative **7** in a 1:1:1 molar ratio in water was vigorously stirred at room temperature for 30 min. After completion of the reaction (TLC analysis), the mixture was filtered to afford the corresponding alkyl 2-(5-hydroxy-2,4,6-trioxohexahydro-5-pyrimidinyl)-3-(alkyl or arylamino)-2-propenoates **8** in high yields. $^1$H and $^{13}$C NMR spectra of the crude products clearly indicated the formation of these novel hydroxy barbiturates **8**. All the products were characterized by FTIR, $^1$H and $^{13}$C NMR spectra, and elemental analysis. The reaction can be represented as in Table 1.

The scope and limitations of this simple process were explored by using two alkyl propiolates, two alloxan derivatives and a wide range of primary amines. A variety of structurally diverse amines underwent the one-pot reaction smoothly without using any catalyst to afford the corresponding barbiturate derivatives in good to high yields. As shown in Table 1, the allylic, benzylic, hindered and unhindered primary amines are used in this protocol with excellent results. Moreover, aromatic primary amines give the corresponding barbiturates in good yields. Thus, a diverse set of biologically useful barbiturate products can be potentially prepared in one step by this method. However, secondary amines such as morpholine and thiomorpholine have not participated in the reaction. We also tried to take advantage of 25% aqueous ammonia, 50% aqueous hydroxylamine and phenylhydrazine as the amine component. Unfortunately, the reaction of alloxan and methyl propiolate with each of these $NH_2$-containing compounds did not afford the desired barbiturate under the same reaction conditions.

Although the mechanism of the reaction between a primary amine and alkyl propiolate in the presence of alloxan has not yet been established experimentally, a plausible explanation is depicted in Figure 2. On the basis of the well established chemistry of trivalent nitrogen nucleophiles, the successful nucleophilic attack by amines on a carbon atom is facilitated when the latter is conjugated with a carbonyl group or when it is part of an unsaturated bond otherwise activated. Therefore, the first step may involve nucleophilic addition of the primary amine to the alkyl propiolate and formation of the β-aminoacrylate **9** as an electron-rich enamine.[16] The central carbonyl groups of the cyclic vicinal triones such as alloxan derivatives possess outstanding electrophilic (electron-pair-accepting) properties.[17] The polar reactions with carbanion-like (electron rich) species such as enamines give rise to nucleophilic addition reactions to carbonyl groups under exclusive C–C bond formation.[18] Subsequent nucleophilic attack of β-aminoacrylate **9** to the central carbonyl group of the alloxan **7** would yield iminium-oxyanion intermediate **10** that can be tautomerized to product **8**.

The key step in the synthesis is an efficient component reaction of a primary amine with an alkyl propiolate to give a β-aminoacrylate derivative, which then reacts with alloxans. In order to confirm the route mechanism of the reaction in Figure 2, via the formation of β-aminoacrylate intermediate in the first stage of the reaction, 3-isobutylaminomethylacrylate **9a** as a representative β-aminoacrylate was synthesized separately by the condensation of isobutylamine and methyl propiolate. Then, we examined the reaction of the isolated 3-isobutylaminomethylacrylate with 1 equiv of alloxan in water and we obtained the product **8a** in 85%.

In conclusion, we have developed a novel one-pot, three-component reaction for the preparation of barbiturates of potential synthetic and pharmacological interest. Excellent yields, a simple purification process, short reaction times, one pot, 100% atom

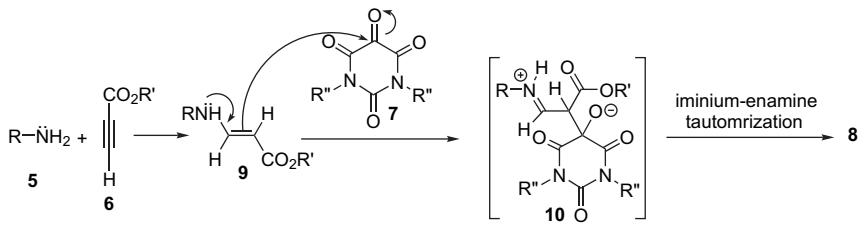



**Figure 2.** Possible mechanism for the formation of products **8**.

efficiency and finally using water as a cheap, nontoxic, environmentally friendly solvent are the main advantages of this method. This method appears to have broad scope with respect to variations of primary amines, alkyl propiolates and alloxan derivatives, and presents a straightforward procedure for the efficient synthesis of novel biologically active barbiturates.

## 3. Experimental

### 3.1. General

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. FTIR 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 $CDCl_3$, $CD_3COCD_3$ or $CD_3SOCD_3$ as solvent and calibrated using residual undeuterated solvent as an internal reference. Analytical TLC was carried out on precoated plates (Merck silica gel 60, $F_{254}$) and visualized with UV light. All chemical reagents were obtained from Aldrich, Merck, Fluka or Acros, and were used without further purification.

### 3.2. Typical procedure for the preparation of methyl 2-(5-hydroxy-2,4,6-trioxohexahydro-5-pyrimidinyl)-3-(isobutylamino)-2-propenoate (8a)

To a magnetically stirred solution of isobutylamine (0.073 g, 1.0 mmol) and methyl propiolate (0.084 g, 1.0 mmol) in water (5 mL) was added alloxan (0.160 g, 1.0 mmol) at room temperature (25 °C) and stirring was continued for about 30 min. The completion of reaction was confirmed by TLC (EtOAc–hexane 2:1). The resulting solid was removed by filtration, washed with water (5 mL) and diethylether (1 mL) and dried at 80 °C in air to give **8a** as a white powder (0.327 g, 72%). The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.

White powder (0.188 g, 82%); mp 200–202 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3335 (O–H), 3300, 3240, 3115 (N–H), 1768, 1704, 1646 (C=O); $\delta_H$ (400.1 MHz, $CDCl_3$) 0.85 (6H, d, *J* 5.2 Hz, $CH(CH_3)_2$), 1.67–1.72 (1H, m, $CH(CH_3)_2$), 3.02 (2H, dd, *J* 5.5, 5.6 Hz, N–$CH_2$), 3.44 (3H, s, $OCH_3$), 7.10 (1H, s, OH), 7.12 (1H, d, *J* 17.1 Hz, =C*H*–NH), 7.72 (1H, br d, =CH–N*H*···O=C), 11.15 (2H, s, N*H*CON*H*); $\delta_C$ (100.7 MHz, $CDCl_3$) 171.8, 167.2, 152.3, 150.6, 91.0, 71.8, 56.5, 50.7, 30.0, 20.5. Anal. Calcd for $C_{12}H_{17}N_3O_6$ (229.28): C, 48.16; H, 5.73; N, 14.04%. Found: C, 48.24; H, 5.70; N, 13.97%.

#### 3.2.1. Methyl 3-(benzylamino)-2-(5-hydroxy-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (8b)

White powder (0.283 g, 85%); mp 180–182 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3277 (O–H), 3113 (N–H), 1769, 1703, 1670 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 3.39 (3H, s, $OCH_3$), 4.41 (2H, d, *J* 5.6 Hz, N–$CH_2$), 7.17 (1H, s, OH), 7.24–7.58 (6H, m, =C*H*–NH and $C_6H_5$), 8.00–8.05 (1H, m, =CH–N*H*···O=C), 11.19 (2H, s, N*H*CON*H*); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 172.3, 167.2, 151.6, 150.6, 140.1, 129.0, 127.8, 127.5, 92.1, 71.9, 52.2, 50.8. Anal. Calcd for $C_{15}H_{15}N_3O_6$ (333.29): C, 54.06; H, 4.54; N, 12.61%. Found: C, 53.97; H, 4.60; N, 12.58%.

#### 3.2.2. Methyl 3-(hexylamino)-2-(5-hydroxy-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (8c)

White powder (0.298 g, 91%); mp 149–151 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3354 (O–H), 3249 (N–H), 1770, 1714, 1670 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 0.84 (3H, t, *J* 7.0 Hz, $CH_2CH_3$), 1.20–1.25 and 1.43–1.48 (8H, 2m, $4CH_2$), 3.18 (2H, dt, *J* 6.5, 6.4 Hz, N–$CH_2$), 3.40 (3H, s, $OCH_3$), 7.10 (1H, s, OH), 7.13 (1H, d, *J* 14.0 Hz, =C*H*–NH), 7.62–7.66 (1H, br m, =CH–N*H*···O=C), 11.15 (2H, s, N*H*CON*H*); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 172.3, 167.1, 151.7, 150.6, 91.1, 71.9, 50.6, 49.0, 31.4, 26.1, 22.5, 14.4. Anal. Calcd for $C_{14}H_{21}N_3O_6$ (327.33): C, 51.37; H, 6.47; N, 12.84%. Found: C, 51.42; H, 6.44; N, 12.87%.

#### 3.2.3. Methyl 3-(phenylamino)-2-(5-hydroxyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (8d)

White powder (0.246 g, 77%); mp 208–210 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3400 (O–H), 3225, 3110 (N–H), 1766, 1729, 1667 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 3.58 (3H, s, $OCH_3$), 6.99–7.34 (5H, m, $C_6H_5$), 7.49 (1H, s, OH), 7.75 (1H, d, *J* 13.4 Hz, =C*H*–NH), 9.48 (1H, d, *J* 13.4 Hz, =CH–N*H*···O=C), 11.32 (2H, s, N*H*CON*H*); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 171.3, 166.9, 150.5, 142.4, 141.2, 130.1, 123.2, 116.3, 97.6, 72.1, 51.5. Anal. Calcd for $C_{14}H_{13}N_3O_6$ (319.27): C, 52.67; H, 4.10; N, 13.16%. Found: C, 52.74; H, 4.01; N, 13.20%.

#### 3.2.4. Methyl 3-(4-hydroxyanilino)-2-(5-hydroxyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (8e)

White powder (0.281 g, 84%); mp 200–202 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3335, 3308 (O–H), 3294 (N–H), 1719, 1701, 1678 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 3.55 (3H, s, $OCH_3$), 6.73 and 7.02 (4H, 2d, *J* 8.8 Hz, $C_6H_4OH$), 7.36 (1H, s, OH), 7.60 (1H, d, *J* 13.6 Hz, =C*H*–NH), 9.23 (1H, s, $C_6H_4OH$), 9.35 (1H, d, *J* 13.6 Hz, =CH–N*H*···O=C), 11.30 (2H, s, N*H*CON*H*); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 171.8, 166.9, 153.9, 150.5, 143.8, 133.4, 118.2, 116.5, 95.7, 72.1, 51.3. Anal. Calcd for $C_{14}H_{13}N_3O_7$ (335.27): C, 50.15; H, 3.91; N, 12.53%. Found: C, 50.10; H, 3.90; N, 12.58%.

#### 3.2.5. Ethyl 2-(5-hydroxy-2,4,6-trioxohexahydro-5-pyrimidinyl)-3-(isobutylamino)-2-propenoate (8f)

White powder (0.248 g, 79%); mp 179–181 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3265 (O–H), 3100 (N–H), 1728, 1705, 1630 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 1.36 (6H, d, *J* 6.7 Hz, $CH(CH_3)_2$), 1.56 (3H, t, *J* 7.1 Hz, $OCH_2CH_3$), 2.22–2.26 (1H, m, $CH(CH_3)_2$), 3.59 (2H, dd, *J* 5.7, 6.9 Hz, N–$CH_2$), 4.39 (2H, q, *J* 6.7 Hz, $OCH_2$), 7.11 (1H, s, OH), 7.72 (1H, d, *J* 13.6 Hz, =C*H*–NH), 8.42 (1H, br d, =CH–N*H*···O=C), 11.16 (2H, s, N*H*CON*H*); $\delta_C$ (100.7 MHz, DMSO-$d_6$+acetone-$d_6$) 172.3, 167.2, 153.2, 150.5, 92.0, 72.5, 59.2, 56.8, 30.4, 19.6, 13.9. Anal. Calcd for $C_{13}H_{19}N_3O_6$ (313.30): C, 49.84; H, 6.11; N, 13.41%. Found: C, 49.90; H, 6.07; N, 13.48%.

#### 3.2.6. Ethyl 3-(benzylamino)-2-(5-hydroxy-1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (8g)

White powder (0.323 g, 93%); mp 170–172 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3323 (O–H), 3212 (N–H), 1723, 1698, 1677 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 1.10 (3H, t, *J* 7.0 Hz, $OCH_2CH_3$), 3.96 (2H, q, *J* 6.6 Hz, $OCH_2$), 4.52 (2H, d, *J* 6.0 Hz, N–$CH_2$), 7.27–7.41 (6H, m, OH+$C_6H_5$), 7.43 (1H, d, *J* 13.6 Hz, =C*H*–NH), 8.23–8.24 (1H, m, =CH–N*H*···O=C), 10.84 (2H, s, N*H*CON*H*); $\delta_C$ (100.7 MHz, DMSO-$d_6$+acetone-$d_6$) 171.8, 166.7, 152.3, 150.2, 139.7, 128.5, 127.5, 127.2, 92.6, 72.0, 58.8, 52.2, 13.9. Anal. Calcd for $C_{16}H_{17}N_3O_6$ (347.32): C, 55.33; H, 4.93; N, 12.10%. Found: C, 55.40; H, 4.95; N, 12.05%.

#### 3.2.7. Ethyl 3-(hexylamino)-2-(5-hydroxy-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (8h)

White powder (0.307 g, 90%); mp 172–174 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3313 (O–H), 3210 (N–H), 1720, 1694, 1661 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 0.82 (3H, br s, $CH_2CH_3$), 1.01 (3H, t, *J* 7.0 Hz, $OCH_2CH_3$), 1.22–1.26 and 1.43–1.47 (8H, 2 m, $4CH_2$), 3.17–3.19 (2H, m, N–$CH_2$), 3.86 (2H, q, *J* 7.0 Hz, $OCH_2CH_3$), 7.06 (1H, s, OH), 7.13 (1H, d, *J* 13.7 Hz, =C*H*–NH), 7.75–7.79 (1H, br m, =CH–N*H*···O=C), 11.16 (2H, s, N*H*CON*H*); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 172.5, 166.6, 152.2, 150.6, 91.1, 71.7, 59.1, 48.9, 31.4, 31.3, 26.1, 22.5, 14.3, 14.1. Anal. Calcd for $C_{15}H_{23}N_3O_6$ (341.36): C, 52.78; H, 6.79; N, 12.31%. Found: C, 52.70; H, 6.73; N, 12.38%.

*3.2.8. Ethyl 3-(propylamino)-2-(5-hydroxy-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (**8i**)*

White powder (0.263 g, 88%); mp 171–175 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3360 (O–H), 3239 (N–H), 1703, 1655 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 0.84 (3H, t, *J* 7.3 Hz, $CH_2CH_3$), 1.01 (3H, t, *J* 7.0 Hz, $OCH_2CH_3$), 1.47–1.51 (2H, m, $CH_2CH_3$), 3.15–3.19 (2H, m, N–$CH_2$), 3.88 (3H, q, *J* 7.0 Hz, $OCH_2CH_3$), 7.08 (1H, s, OH), 7.15 (1H, d, *J* 13.9 Hz, =CH–NH), 7.79–7.83 (1H, br m, =CH–NH···O=C), 11.18 (2H, s, NHCONH); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 172.5, 166.6, 152.3, 150.6, 91.1, 79.6, 71.6, 59.1, 50.6, 24.6, 14.2, 11.4. Anal. Calcd for $C_{12}H_{17}N_3O_6$ (299.28): C, 48.16; H, 5.73; N, 14.04%. Found: C, 48.22; H, 5.66; N, 13.98%.

*3.2.9. Ethyl 3-(adamantylamino)-2-(5-hydroxyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (**8j**)*

White powder (0.317 g, 81%); mp 232–234 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3344 (O–H), 3235 (N–H), 1730, 1703, 1655 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 1.02 (3H, t, *J* 7.0 Hz, $OCH_2CH_3$), 1.62 and 1.73 (12H, 2br s, $2CH_2$ of adamantyl), 2.07 (3H, br s, 3CH of adamantyl), 3.86 (3H, q, *J* 7.0 Hz, $OCH_2CH_3$), 7.10 (1H, s, OH), 7.38 (1H, d, *J* 14.0 Hz, =CH–NH), 7.93–7.96 (1H, m, =CH–NH···O=C), 11.18 (2H, s, NHCONH); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 172.4, 166.6, 150.6, 146.7, 91.4, 71.8, 59.2, 52.1, 43.3, 35.9, 29.3, 14.1. Anal. Calcd for $C_{19}H_{25}N_3O_6$ (391.42): C, 58.30; H, 6.44; N, 10.74%. Found: C, 58.37; H, 6.40; N, 10.80%.

*3.2.10. Ethyl 3-(allylamino)-2-(5-hydroxyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (**8k**)*

White powder (0.283 g, 95%); mp 162–164 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3371 (O–H), 3280 (N–H), 1720, 1700, 1682 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 1.02 (3H, t, *J* 7.0 Hz, $OCH_2CH_3$), 3.84–3.90 (4H, m, $OCH_2CH_3$ and $NCH_2$), 5.12 and 5.17 (2H, 2dd, *J* 17.2, 10.2, 1.6 Hz, –CH=$CH_2$), 5.85–5.89 (1H, m, –CH=$CH_2$), 7.11 (1H, s, OH), 7.15 (1H, d, *J* 13.8 Hz, =CH–NH), 7.80–7.84 (1H, m, =CH–NH···O=C), 11.18 (2H, s, NHCONH); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 172.4, 166.6, 151.9, 150.6, 136.5, 116.6, 92.1, 71.7, 59.2, 50.7, 14.2. Anal. Calcd for $C_{12}H_{15}N_3O_6$ (297.26): C, 48.49; H, 5.09; N, 14.14%. Found: C, 48.55; H, 5.02; N, 14.18%.

*3.2.11. Ethyl 3-(phenylamino)-2-(5-hydroxyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (**8l**)*

White powder (0.253 g, 76%); mp 190–192 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3393 (O–H), 3300, 3203, 3094 (N–H), 1764, 1733, 1632 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 1.08–1.12 (3H, m, $CH_3$), 3.96–4.02 (2H, m, $OCH_2$), 6.98–7.33 (5H, m, $C_6H_5$), 7.46 (1H, s, OH), 7.78 (1H, d, *J* 13.1 Hz, =CH–NH), 9.68 (1H, d, *J* 13.1 Hz, =CH–NH···O=C), 11.39 (2H, s, NHCONH); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 171.3, 167.1, 150.5, 142.9, 141.0, 130.1, 123.2, 116.1, 97.6, 71.9, 60.1, 14.0. Anal. Calcd for $C_{15}H_{15}N_3O_6$ (333.29): C, 54.06; H, 4.54; N, 12.61%. Found: C, 53.97; H, 4.47; N, 12.54%.

*3.2.12. Methyl 3-(benzylamino)-2-(5-hydroxy-1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (**8m**)*

White powder (0.289 g, 80%); mp 140–142 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3354 (O–H), 1749, 1705, 1669 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 3.12 (6H, s, $2NCH_3$), 3.40 (3H, s, $OCH_3$), 4.39 (2H, d, *J* 5.9 Hz, N–$CH_2$), 7.23–7.36 (5H, m, $C_6H_5$), 7.41 (1H, s, OH), 7.56 (1H, d, *J* 14.0 Hz, =CH–NH), 7.64–7.70 (1H, m, =CH–NH···O=C); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 170.5, 167.6, 152.7, 151.5, 140.1, 129.0, 127.7, 127.6, 93.8, 75.3, 51.9, 51.0, 28.9. Anal. Calcd for $C_{17}H_{19}N_3O_6$ (361.35): C, 56.51; H, 5.30; N, 11.63%. Found: C, 56.60; H, 5.35; N, 11.60%.

*3.2.13. Methyl 3-(hexylamino)-2-(5-hydroxy-1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (**8n**)*

White powder (0.316 g, 89%); mp 86–88 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3561 (O–H), 3475 (N–H), 1683, 1610 (C=O); $\delta_H$ (400.1 MHz, $CDCl_3$) 0.85 (3H, t, *J* 5.0 Hz, $CH_2CH_3$), 1.26–1.30 and 1.53–1.58 (8H, 2m, $4CH_2$), 3.20–3.24 (2H, m, N–$CH_2$), 3.29 (6H, s, $2NCH_3$), 3.55 (3H, s, $OCH_3$), 7.24 (1H, s, OH), 7.50 (1H, d, *J* 13.9 Hz, =CH–NH), 7.96–8.02 (1H, m, =CH–NH···O=C); $\delta_C$ (100.7 MHz, $CDCl_3$) 170.8, 166.8, 153.3, 151.2, 92.1, 72.3, 51.1, 49.6, 31.4, 31.0, 29.0, 26.2, 22.5, 14.0. Anal. Calcd for $C_{16}H_{25}N_3O_6$ (355.38): C, 54.08; H, 7.09; N, 11.82%. Found: C, 54.05; H, 7.14; N, 11.77%.

*3.2.14. Methyl 3-(allylamino)-2-(5-hydroxyl-1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (**8o**)*

White powder (0.280 g, 90%); mp 126–128 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3563 (O–H), 3460 (N–H), 1730, 1704, 1666 (C=O); $\delta_H$ (400.1 MHz, acetone-$d_6$) 3.20 (6H, s, $2NCH_3$), 3.49 (3H, s, $OCH_3$), 3.93–3.96 (2H, m, N–$CH_2$), 5.14 and 5.24 (2H, 2dd, *J* 17.1, 10.2, 1.5 Hz, –CH=$CH_2$), 5.77 (1H, s, OH), 5.92–5.96 (1H, m, –CH=$CH_2$), 7.39 (1H, d, *J* 13.8 Hz, =CH–NH), 7.84–7.88 (1H, br m, =CH–NH···O=C); $\delta_C$ (100.7 MHz, DMSO-$d_6$+acetone-$d_6$) 170.4, 152.5, 151.8, 135.8, 115.7, 115.4, 50.8, 50.7, 50.5, 50.0, 28.0. Anal. Calcd for $C_{13}H_{17}N_3O_6$ (311.29): C, 50.16; H, 5.50; N, 13.50%. Found: C, 50.21; H, 5.53; N, 13.46%.

*3.2.15. Ethyl 2-(5-hydroxy-1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-3-(isobutylamino)-2-propenoate (**8p**)*

White powder (0.256 g, 75%); mp 106–108 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3337 (O–H), 1700, 1672, 1609 (C=O); $\delta_H$ (400.1 MHz, DMSO-$d_6$) 0.84 (6H, d, *J* 6.6 Hz, $CH(CH_3)_2$), 0.92 (3H, t, *J* 7.1 Hz, $OCH_2CH_3$), 1.68–1.73 (1H, m, $CH(CH_3)_2$), 3.04 (2H, dd, *J* 5.7, 5.9 Hz, N–$CH_2$), 3.13 (6H, s, $2NCH_3$), 3.82 (2H, q, *J* 6.6 Hz, $OCH_2$), 7.15 (1H, s, OH), 7.22 (1H, d, *J* 13.9 Hz, =CH–NH), 7.90 (1H, br d, *J* 6.4 Hz, =CH–NH···O=C); $\delta_C$ (100.7 MHz, DMSO-$d_6$) 170.5, 167.0, 152.9, 151.5, 91.7, 72.0, 59.1, 59.0, 30.0, 28.9, 19.9, 14.3. Anal. Calcd for $C_{15}H_{23}N_3O_6$ (341.36): C, 52.78; H, 6.79; N, 12.31%. Found: C, 52.81; H, 6.83; N, 12.27%.

*3.2.16. Ethyl 3-(benzylamino)-2-(5-hydroxy-1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (**8q**)*

White powder (0.316 g, 84%); mp 143–145 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3409 (O–H), 3295 (N–H), 1693, 1665, 1629 (C=O); $\delta_H$ (400.1 MHz, $CDCl_3$) 1.06 (3H, t, *J* 7.0 Hz, $CH_2CH_3$), 3.27 (6H, s, $2NCH_3$), 3.97 (2H, q, *J* 7.0 Hz, $OCH_2CH_3$), 4.41 (2H, d, *J* 5.7 Hz, N–$CH_2$), 7.22–7.33 (6H, m, $C_6H_5$ and OH), 7.60 (1H, d, *J* 13.6 Hz, =CH–NH), 8.35–8.41 (1H, br m, =CH–NH···O=C); $\delta_C$ (100.7 MHz, $CDCl_3$) 170.8, 166.4, 153.2, 151.0, 137.7, 128.8, 127.8, 127.2, 93.1, 72.2, 59.6, 53.2, 28.9, 14.2. Anal. Calcd for $C_{18}H_{21}N_3O_6$ (375.37): C, 57.59; H, 5.64; N, 11.19%. Found: C, 57.64; H, 5.67; N, 11.24%.

*3.2.17. Ethyl 3-(phenylamino)-2-(5-hydroxy-1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2-propenoate (**8r**)*

White powder (0.260 g, 72%); mp 124–126 °C; FTIR (KBr) ($\nu_{max}$, $cm^{-1}$): 3377 (O–H), 1705, 1668 (C=O), 1599 (C=C); $\delta_H$ (400.1 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7.0 Hz, $CH_2CH_3$), 3.27 (6H, s, $2NCH_3$), 3.97 (2H, q, *J* 7.0 Hz, $OCH_2CH_3$), 6.98–7.34 (6H, m, $C_6H_5$ and OH), 8.06 (1H, d, *J* 13.4 Hz, =CH–NH), 9.90 (1H, d, *J* 13.4 Hz, =CH–NH···O=C); $\delta_C$ (100.7 MHz, $CDCl_3$) 170.50, 166.11, 150.84, 144.72, 140.00, 129.60, 123.56, 116.20, 96.78, 72.24, 60.16, 29.00, 14.06. Anal. Calcd for $C_{17}H_{19}N_3O_6$ (361.35): C, 56.51; H, 5.30; N, 11.63%. Found: C, 56.46; H, 5.34; N, 11.68%.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.039.

## References and notes


1. Bojarski, J. T.; Mokrosz, J. L.; Barton, H. J.; Paluchowska, M. H. *Adv. Heterocycl. Chem.* **1985**, *38*, 229–297.
2. In *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 9th ed.; Delgado, J. N., Remers, W. A., Lippincott, J. B., Eds.; Wolters Kluwer Health: Philadephia, PA, 1991.
3. Grams, F.; Brandstetter, H.; D'Alò, S.; Geppert, D.; Krell, H.-W.; Leinert, H.; Livi, V.; Menta, E.; Oliva, A.; Zimmermann, G. *Biol. Chem.* **2001**, *382*, 1277–1285.
4. Foley, L. H.; Palermo, R.; Dunten, P.; Wang, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 969–972.
5. Lein, M.; Jung, K.; Ortel, B.; Stephan, C.; Rothaug, W.; Juchem, R.; Johannsen, M.; Deger, S.; Schnorr, D.; Loening, S.; Krell, H.-W. *Oncogene* **2002**, *21*, 2089–2096.
6. Mangoldt, D.; Sinn, B.; Lein, M.; Krell, H. W.; Schnorr, D.; Loening, S. A.; Jung, K. *Apoptosis* **2002**, *7*, 217–220.
7. Daniewski, A. R.; Liu, W.; Okabe, M. *Org. Process Res. Dev.* **2004**, *8*, 411–414.
8. (a) Mironov, M. A. *QSAR Comb. Sci.* **2006**, *25*, 423–431; (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634; (d) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499.
9. Lancaster, M. *Green Chemistry: An Introductory Text*; Royal Society of Chemistry: Cambridge, 2002.
10. Bezdek, R. H.; Wendling, R. M.; DiPerna, P. *J. Environ. Manage.* **2008**, *86*, 63–79.
11. (a) Dolle, R. E.; Bourdonnec, B. L.; Morales, G. A.; Moriarty, K. J.; Salvino, J. M. *J. Comb. Chem.* **2006**, *8*, 597–635; (b) Ganesan, A. *Comb. Chem.* **2002**, *7*, 47–55.
12. (a) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304–322; (b) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screen.* **2001**, *4*, 1–34; (c) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005.
13. (a) Teimouri, M. B.; Khavasi, H. R. *Tetrahedron* **2007**, *63*, 10269–10275; (b) Teimouri, M. B. *Tetrahedron* **2006**, *62*, 10849–10853; (c) Teimouri, M. B.; Bazhrang, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3697–3701; (d) Teimouri, M. B.; Shaabani, A.; Bazhrang, R. *Tetrahedron* **2006**, *62*, 1845–1848; (e) Teimouri, M. B.; Bazhrang, R.; Eslamimanesh, V.; Nouri, A. *Tetrahedron* **2006**, *62*, 3016–3020.
14. Sheldon, R. G. *Green Chem.* **2005**, *7*, 267–278.
15. (a) Pirrung, M. C. *Chem.—Eur. J.* **2006**, *12*, 1312–1317; (b) Mironov, M. A.; Ivantsova, M. N.; Tokareva, M. I.; Mokrushin, V. S. *Tetrahedron Lett.* **2005**, *46*, 3957–3960; (c) Pirrung, M. C.; Sarma, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 444–445; (d) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299–307.
16. Azizian, J.; Hatamjafari, F.; Karimi, A. R.; Shaabanzadeh, M. *Synthesis* **2006**, 765–767.
17. Rubin, M. B.; Gleiter, R. *Chem. Rev.* **2000**, *100*, 1121–1164.
18. Schank, K.; Lieder, R.; Lick, C.; Glock, R. *Helv. Chem. Acta* **2004**, *87*, 869–924.