Tandem Aldol-Michael reactions in aqueous diethylamine medium: a greener and efficient approach to dimedone-barbituric acid derivatives

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Abstract

Background: Green chemistry is a rapidly developing new field that provides us with a proactive avenue for the sustainable development of future science and technologies. Green chemistry uses highly efficient and environmentally benign synthetic protocols to deliver lifesaving medicines, accelerating lead optimization processes in drug discovery, with reduced unnecessary environmental impact. From this viewpoint, it is desirable to use water instead of organic solvents as a reaction medium, since water is safe, abundant and an environmentally benign solvent.

Results: A convenient one-pot method for the efficient synthesis of the novel Zwitterion derivatives 4a-p via a three-component condensation reaction of barbituric acid derivatives 1a,b, dimedone 2, and various aldehydes 3 in the presence of aqueous diethylamine media is described. This new approach is environmentally benign, with clean synthetic procedure, short reaction times and easy work-up procedure which proceeded smoothly to provide excellent yield (88-98%). The synthesized products were characterized by elemental analysis, IR, MS, NMR and CHN analysis. The structure of 4a was further confirmed by single crystal X-ray diffraction. The compound crystallizes in the orthorhombic space group Pbca with α = 14.6669 (5) Å, b = 18.3084 (6) Å, c = 19.0294 (6) Å, α = 90°, β = 90°, γ = 90°, V = 5109.9 (3) Å³, and Z = 8. The molecules are packed in crystal structure by weak intermolecular C–H⋯O hydrogen bonding interactions.

Conclusions: An environmentally benign Aldol-Michael protocol for the synthesis of dimedone-barbituric derivatives using aqueous diethylamine medium is achieved.

Keywords: Tandem Aldol-Michael reactions, MCRs, Barbituric acid, Aqueous media, Green chemistry, Dimedone, Zwitterions

Background

Recently, the development of environmentally benign and clean synthetic procedures has become the goal of organic synthesis. Water plays an essential role in life processes and also as a medium for organic reactions [1,2]. The use of water as a reaction medium exhibits remarkable benefit because of its high polarity and therefore immiscibility with most organic compounds. Reactions in aqueous media are environmentally safe and have less carcinogenic effects with a simple work up procedure which are especially important in industry. Thus, there is a need for developing multicomponent reactions (MCR’s) in water, without the use of any harmful organic solvents.

On the other hand, due to the diverse biological properties of barbituric acid derivatives (1), there is a widespread interest in their synthesis [3-7]. Compounds alkylated in the fifth position have demonstrated anticancer, HIV-1 and HIV-2 protease inhibitors [8], sedative-hypnotic [9,10] and anticonvulsant [11] properties. Many of their representatives have clinical use as anti-inflammatory [12] and hypnotic drugs, such as veronal, phenobarbital, secobarbital, boculone and sodium pentothal (Figure 1) [13-15]. A
number of compounds having these systems have been synthesized with diverse pharmacological activities [16,17].

Dimedone (5,5-dimethylcyclohexane-1,3-dione) 2 belongs to the cyclic 1,3-diketones – a very important class of organic compounds. A wide range of practical applications of dimedone include their uses as versatile precursors for synthesis of numerous hetero and spirocyclic compounds [18], xanthene derivatives with their industrial [19] and synthetic [20] applications, and also as reagent for various analytical determinations [21].

As a part of our work on one-pot multicomponent reactions (MCRs) for the synthesis of various heterocyclic compounds, we report here a highly efficient procedure for the preparation of dimedone-barbituric derivatives based on tandem Aldol-Michael reactions using aqueous diethylamine medium.

Results and discussion

In a typical experimental procedure, a mixture of barbituric acid 1a,b, dimedone 2 and aromatic aldehyde 3 in water was stirred in the presence of a stoichiometric amount of diethylamine (1.0 equiv.) to afford the ‘Zwitterion adduct’ salts of dimedone-barbituric acid derivative 4a in high yields (Scheme 1).

A possible mechanism for the tandem Aldol- Michael reaction is shown in Figure 2. In the first step of the reaction, olefin is produced by an Aldol condensation between aryl aldehyde 3 and 1a,b promoted by DEA. Dimedone in the presence of DEA is then converted to its corresponding diethylammonium dimedonate that easily reacts with olefin to give product 4a-p [22-31].

In the absence of DEA, the reaction does not proceed efficiently and only a poor yield of products was obtained after 10 h. The structures of products were confirmed by physical and spectroscopic (IR, MS, NMR) data, and by elemental analysis. The workup procedure is very simple and the products do not require further purification.

Conclusions

In summary, a mild, efficient, and expeditious method has been developed for the synthesis of zwitterion-condensed products 4a-p via a three component; one-pot cyclocondensation reaction of aromatic aldehyde, barbituric acid, and dimedone using aqueous diethylamine medium. The main advantage of the present methodology is a simple work-up procedure with milder reaction conditions. This method provides excellent yields of the products with high selectivity. Further studies on expanding the application of this method and the biological evaluation of these dimedone-barbituric derivatives are in progress.

Experimental section

General

All chemicals were purchased from Aldrich, Sigma-Aldrich, Fluka etc., and were used without further purification,
unless otherwise stated. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. The NMR spectra were recorded on a Jeol-400 NMR spectrometer. $^1$H NMR (400 MHz), and $^{13}$C NMR (100 MHz) were run in either deuterated dimethylsulphoxide (DMSO-$d_6$) or deuterated chloroform (CDCl$_3$). Chemical shifts (δ) are referred in terms of ppm and $J$-coupling constants are given in Hz. Mass spectra were recorded on a Jeol of JMS-600H. Elemental analysis was carried out on an Elmer 2400 Elemental Analyzer; CHN mode.

**General procedure for aldol condensation Michael addition for the synthesis of 4a-p (GP1)**

A mixture of aldehyde 3 (1.5 mmol), dimedone 2 (1.5 mmol), barbituric acid derivatives 1a,b (1.5 mmol) and Et$_2$NH (1.5 mmol, 155 μL) in 1.5 mL of degassed H$_2$O was stirred at room temperature for 1–2 hours until TLC showed complete disappearance of the reactants. The product precipitated and the mixture was filtered and washed with ether (3 x 20 mL). The solid was recrystallized from a mixture of CH$_2$Cl$_2$/Et$_2$O to afford pure product 4a-p.

$5$-((2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(phenyl)methyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (4a)

4a was prepared from 1,3-dimethylbarbituric acid 1a, dimedone 2 and benzaldehyde according to the general procedure (GP1) yielding colorless crystalline material (671 mg, 1.47 mmol, 98%). m.p: 159°C; IR (KBr, cm$^{-1}$): 3150, 2959, 1667, 1617, 1585, 1422, 1256, 1227; $^1$H NMR (400 MHz, CDCl$_3$): δ 15.28 (s, 1H, OH), 7.17-7.04 (m, 5H, Ph), 5.85 (s, 1H, benzyl-H), 3.29 (s, 12H, 4CH$_3$), 2.96 (q, 4H, $J$ = 7.3 Hz, CH$_2$CH$_3$), 2.29 (m, 2H, CH$_2$), 1.24 (t, 6H, $J$ = 7.3 Hz, CH$_3$CH$_2$)$_2$, 1.14 (s, 3H, CH$_3$), 1.05 (s, 3H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 192.5, 180.8, 152.5, 142.5, 128.0, 126.7, 125.1, 116.3, 90.9, 51.4, 45.9, 42.2, 33.0, 31.5, 29.6, 28.4, 27.6, 11.4;
LC/MS (ESI): 457 [M]+; Anal. for C_{25}H_{35}N_{3}O_{5}; calcd: C, 65.62; H, 7.71; N, 9.18; Found: C, 65.61; H, 7.73; N, 9.20.

The structure of 4a was confirmed by X-ray crystal structure analysis. CCDC- 933624 contains the supplementary crystallographic data for this compound. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A colorless crystal suitable for X-ray analysis was obtained from recrystallization of the compound from CHCl₃/Et₂O at room temperature after 2 days.

5-((2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(p-tolyl)methyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidine 4-olate (4b)

4b was prepared from 1,3-dimethylbarbituric acid 1a, dimedone 2 and p-tolualdehyde according to the general procedure (GP1) yielding an oily material (685 mg, 1.45 mmol, 97%). IR (KBr, cm⁻¹): 3150, 2954, 2867, 1675, 1580, 1447, 1380, 1256, 1145;¹H NMR (400 MHz, CDCl₃): δ 15.25 (s, 1H, OH), 7.00-6.93 (m, 4H, Ph), 5.84 (s, 1H, benzyl-H), 3.28 (s, 12H, 4CH₃), 2.90 (q, J = 7.3 Hz, CH₂CH₃), 2.30 (d, J = 5.1 Hz, CH₂), 2.22 (s, 3H, CH₃), 1.20 (t, J = 7.3 Hz, CH₂CH₃), 1.16 (s, 3H, CH₃), 1.04 (s, 3H, CH₂);¹³C NMR (100 MHz, CDCl₃): δ = 196.5, 180.1, 152.8, 140.5, 134.2, 129.8, 128.7, 126.8, 126.7, 115.6, 91.0, 51.4, 45.9, 42.5, 32.6, 31.5, 29.6, 28.4, 27.6, 20.9, 11.9; LC/MS (ESI): 471 [M]+; Anal. for C_{26}H_{37}N_{3}O_{5}: calcd: C, 66.22; H, 7.91; N, 8.91; Found: C, 66.24; H, 7.92; N, 8.87.

5-((4-Chlorophenyl)(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidine 4-olate (4c)

4c was prepared from 1,3-dimethylbarbituric acid 1a, dimedone 2 and p-chlorobenzaldehyde 3 according to the general procedure (GP1) yielding an oily material (715 mg, 1.45 mmol, 97%). IR (KBr, cm⁻¹): 3151, 2955, 2868, 2497, 1675, 1580, 1444, 1379, 1258, 1206;¹H NMR (400 MHz, CDCl₃): δ 15.02 (s, 1H, OH), 7.12-6.95 (m, 4H, Ph), 5.87 (s, 1H, benzyl-H), 3.30 (s, 12H, 4CH₃), 2.90 (q, J = 7.3 Hz, CH₂CH₃), 2.38 (s, 4H, CH₂), 1.20 (t, J = 7.3 Hz, CH₂CH₃), 1.16 (s, 3H, CH₃), 1.04 (s, 3H, CH₂);¹³C NMR (100 MHz, CDCl₃): δ = 198.1, 181.0, 152.5, 141.5, 130.6, 128.3, 128.0, 127.9, 115.2, 90.7, 65.9, 49.8, 42.3, 32.4, 31.5, 31.2, 29.6, 28.4, 27.6, 15.3, 11.4; LC/MS (ESI): 492 [M]+; Anal. for C_{25}H_{34}ClN_{3}O_{5}: calcd: C, 61.03; H, 6.97; Cl, 7.21; N, 8.54; Found: C, 61.06; H, 7.00; Cl, 7.18; N, 8.57.

5-((4-Bromophenyl)(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidine 4-olate (4d)

4d was prepared from 1,3-dimethylbarbituric acid 1a, dimedone 2 and p-bromobenzaldehyde 3 according to the
general procedure (GP1) yielding an oily material (761 mg, 1.42 mmol, 95%). IR (KBr, cm⁻¹): 3155, 2955, 2867, 2500, 1674, 1579, 1430, 1376, 1204;²H NMR (400 MHz, CDCl₃): δ 15.20 (s, 1H, OH), 7.34 (d, 2H, J = 8.0 Hz, Ph), 6.98 (d, 2H, J = 8.0 Hz, Ph), 5.79 (s, 1H, benzyl-H), 3.27 (s, 12H, 4CH₃), 2.99 (q, 4H, J = 7.3 Hz, CH₂CH₃), 2.40 (d, 2H, J = 5.1 Hz, CH₂), 2.28 (m, 2H, CH₂), 1.29 (t, 6H, J = 7.3 Hz, CH₂CH₃), 1.18 (s, 3H, CH₃), 1.04 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 199.1, 191.2, 164.8, 152.4, 142.8, 132.5, 131.0, 129.9, 128.7, 128.6, 118.9, 115.9, 90.6, 51.2, 45.8, 42.3, 32.7, 31.5, 29.5, 28.5, 28.3, 27.6, 11.4; LC/MS (ESI): 536 [M]+; Anal. for C₂₂H₂₃BrN₂O₅; calcd: C, 55.97; H, 6.39; Br, 14.89; N, 7.83; Found: C, 56.00; H, 6.40; Br, 14.89; N, 7.83.

5-((3-Bromophenyl)(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (4e)

4e was prepared from 1,3-dimethylbarbituric acid 1a, dimedone 2 and m-bromobenzaldehyde 3 according to the general procedure (GP1) yielding an oily material (745 mg, 1.39 mmol, 93%). IR (KBr, cm⁻¹): 3050, 2955, 2868, 2500, 1675, 1581, 1444, 1378, 1255, 1205;¹H NMR (400 MHz, CDCl₃): δ 15.63 (s, 1H, OH), 7.22 (d, 1H, J = 7.3 Hz, Ph), 7.19 (s, 1H, Ph), 7.07 (d, 1H, J = 7.3 Hz, Ph), 7.05 (d, 1H, J = 7.3 Hz, Ph), 5.84 (s, 1H, benzyl-H), 3.34 (s, 6H, 2CH₃), 3.32 (s, 6H, 2CH₃), 2.98 (q, 4H, J = 7.3 Hz, CH₂CH₃), 2.31 (d, 4H, J = 5.1 Hz, CH₂), 1.24 (t, 6H, J = 7.3 Hz, CH₂CH₃), 1.12 (s, 3H, CH₃), 1.03 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 190.8, 186.4, 165.2, 164.4, 151.7, 144.7, 129.7, 129.6, 128.7, 125.3, 91.5, 42.1, 34.4, 28.9, 28.7, 11.5; LC/MS (ESI): 536 [M]+; Anal. for C₂₂H₂₃BrN₂O₅; calcd: C, 55.97; H, 6.39; Br, 14.89; N, 7.83; Found: C, 56.01; H, 6.41; Br, 14.86; N, 7.84.

5-((2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(4-methoxyphenyl)methyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (4f)

4f was prepared from 1,3-dimethylbarbituric acid 1a, dimedone 2 and anisaldehyde 3 according to the general procedure (GP1) yielding an oily material (672 mg, 1.38 mmol, 92%). IR (KBr, cm⁻¹): 3047, 2953, 2866, 2499, 1679, 1577, 1510, 1427, 1373, 1255, 1214;¹H NMR (400 MHz, CDCl₃): δ 15.26 (s, 1H, OH), 6.98 (d, 2H, J = 8.0 Hz, Ph), 6.72 (d, 2H, J = 8.0 Hz, Ph), 5.69 (s, 1H, benzyl-H), 3.71 (s, 3H, CH₃), 3.29 (s, 12H, 4CH₃), 1.19 (t, 6H, J = 7.3 Hz, CH₂CH₃), 1.12 (s, 3H, CH₃), 1.03 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 195.1, 187.2, 157.1, 134.5, 133.9, 127.8, 127.6, 115.6, 113.4,
Table 1 Crystallographic data and refinement information of 4a

| Empirical formula          | C_{25}H_{32}N_{2}O_{6} |
|----------------------------|------------------------|
| Formula weight             | 456.53                 |
| Temperature (K)            | 293                    |
| Crystal system             | Orthorhombic           |
| Space group                | Pbc a                  |
| Cu Ka radiation, λ         | 1.54178 Å              |
| a                          | 14.6669 (5) Å          |
| b                          | 18.3084 (6) Å          |
| c                          | 19.0294 (6) Å          |
| α                          | 90°                    |
| β                          | 90°                    |
| γ                          | 90°                    |
| V                          | 5109.9 (3) Å³         |
| Z                          | 8                      |
| Theta for range for data collection | 3.0-69.2°   |
| μ                          | 0.70 mm⁻¹              |
| Density calc. (g/cm³)      | 1.187                  |
| Crystal shape and colour   | Plate, colourless     |
| Crystal size               | 0.89 x 0.78 x 0.22 mm |
| h/k/l                      | -17.17/22.22/-22.23   |
| Measured reflections       | 32924                  |
| Independent reflections    | 4796 (R(int) = 0.088)  |
| Goodness-of-fit on P²      | 1.04                   |
| R(P² > 2σ(P²)) =           | 0.067                  |
| wR(P²)                     | 0.195                  |
| Δρmax                      | 0.47 e Å⁻³             |
| Δρmin                      | -0.40 e Å⁻³            |

5.2, 4.26, 31.5, 31.1, 27.9, 12.2; LC/MS (ESI): 487 [M⁺]; Anal. for C_{25}H_{33}Cl_{2}N_{3}O_{5}; calcd: C, 64.05; H, 7.65; N, 8.62; Found: C, 64.11; H, 7.64; N, 8.59.

5-(5-(2,4-Dichlorophenyl)-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-1,3-dimethyl-2,6-dioxo-1,2,3, 6-tetrahydroprymidin-4-olate (4 h)

4 h was prepared from 1,3-dimethylbarbituric acid 1a, dimedone 2 and 2,4-dichlorobenzaldehyde 3 according to the general procedure (GP1) yielding a beige solid material (710 mg, 1.35 mmol, 90%). m.p: 148°C; IR (KBr, cm⁻¹): 3050, 2955, 2869, 2728, 2494, 1676, 1575, 1428, 1372, 1238, 1196; H NMR (400 MHz, CDCl₃): δ 14.80 (s, 1H, OH), 7.29 (d, 1H, J = 8.0 Hz, Ph), 7.19 (s, 1H, Ph), 7.12 (d, 2H, J = 8.0 Hz, Ph), 5.76 (s, 1H, benzyl-H), 3.28 (s, 12H, 4CH₃), 3.07 (q, 4H, CH₂CH₂), 2.37 (s, 2H, CH₂), 2.27 (d, 2H, J = 5.1 Hz, CH₂), 1.34 (t, 6H, J = 7.3 Hz, CH₂CH₂), 1.04 (s, 3H, CH₃), 1.01 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 199.1, 165.4, 164.4, 152.5, 139.8, 133.6, 131.7, 131.2, 129.3, 126.4, 115.7, 89.8, 51.2, 45.7, 41.9, 32.4, 31.2, 28.3, 28.2, 11.3; LC/MS (ESI): 526 [M⁺]; Anal. for C_{25}H_{33}Cl_{2}N_{3}O_{5}·calcd: C, 57.04; H, 6.32; Cl, 13.47; N, 7.98; Found: C, 57.09; H, 6.31; Cl, 13.44; N, 8.01.

5-(5-(2,4-Dichlorophenyl)-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-1,3-dimethyl-2,6-dioxo-1,2,3, 6-tetrahydroprymidin-4-olate (4i)

4i was prepared from 1,3-dimethylbarbituric acid 1a, dimedone 2 and p-nitrobenzaldehyde 3 according to the general procedure (GP1) yielding an oily material (702 mg, 1.33 mmol, 89%). IR (KBr, cm⁻¹): 3048, 2955, 2869, 2728, 2494, 1676, 1575, 1428, 1372, 1238, 1196; H NMR (400 MHz, CDCl₃): δ 14.80 (s, 1H, OH), 7.36 (d, 2H, J = 8.0 Hz, Ph), 7.29 (t, 1H, J = 8.0 Hz, Ph), 7.12 (d, 2H, J = 8.0 Hz, Ph), 5.98 (s, 1H, benzyl-H), 3.26 (s, 12H, 4CH₃), 2.92 (q, 4H, CH₂CH₂), 2.37 (s, 2H, CH₂), 2.27 (d, 2H, J = 5.1 Hz, CH₂), 1.42 (t, 6H, J = 7.3 Hz, CH₂CH₂), 1.04 (s, 3H, CH₃), 1.01 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 192.8, 188.9, 165.3, 164.3, 152.5, 149.7, 137.4, 131.5, 129.8, 126.5, 124.2, 115.5, 114.7, 89.9, 53.5, 41.4, 31.9, 28.7, 28.2, 11.4; LC/MS (ESI): 526 [M⁺]; Anal. for C_{25}H_{33}Cl_{2}N_{3}O_{5}·calcd: C, 57.04; H, 6.32; Cl, 13.47; N, 7.98; Found: C, 57.08; H, 6.30; Cl, 13.45; N, 8.00.
5-((2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl) (naphthalen-2-yl)methyl)-1,3-dimethyl-2,6-dioxo-1,2,3, 6-tetrahydropyrimidin-4-olate (4j)

4j was prepared from 1,3-dimethylbarbituric acid 1a, dimedone 2 and 2-naphthaldehyde 3 according to the general procedure (GP1) yielding a white solid material (715 mg, 1.41 mmol, 94%). m.p: 170 °C; IR (KBr, cm\(^{-1}\)): 2994, 2948, 2866, 2506, 1742, 1651, 1603, 1570, 1526, 1473, 1431, 1362, 1245; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 14.26 (s, 1H, OH), 7.46-7.22 (m, 7H, naphthyl), 6.20 (s, 1H, benzyl-H), 3.26 (s, 6H, 2CH\(_3\)), 3.23 (s, 6H, 2CH\(_3\)), 3.14 (q, 4H, \(J = 7.3\) Hz, C\(_2\)H\(_2\)CH\(_3\)), 2.41 (q, 4H, \(J = 5.1\) Hz, CH\(_2\)), 2.23 (s, 2H, CH\(_2\)), 1.37 (t, 6H, \(J = 7.3\) Hz, CH\(_2\)C\(_3\)H\(_3\)), 1.07 (s, 3H, CH\(_3\)), 1.01 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) = 199.0, 180.5, 165.3, 164.3, 152.5, 149.7, 136.8, 131.5, 129.9, 126.5, 124.2, 115.5, 114.7, 89.9, 50.9, 45.5, 41.7, 31.3, 30.7, 28.2, 11.1; LC/MS (ESI): 507 [M]+; Anal. for C\(_{29}\)H\(_{37}\)N\(_3\)O\(_5\): calcd: C, 68.62; H, 7.35; N, 8.28; Found: C, 68.65; H, 7.34; N, 8.30.

5-((2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl) (4-hydroxyphenyl)methyl)-1,3-dimethyl-2,6-dioxo-1,2,3, 6-tetrahydropyrimidin-4-olate (4k)

4k was prepared from 1,3-dimethylbarbituric acid 1a, dimedone 2 and p-hydroxybenzaldehyde 3 according to the general procedure (GP1) yielding a white solid material (645 mg, 1.36 mmol, 91%). m.p: 162°C; IR (KBr, cm\(^{-1}\)): 3017, 2939, 2884, 1747, 1574, 1530, 1506, 1466, 1384, 1241; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 14.52 (s, 1H, OH), 8.50 (brs, 1H, OH), 6.76 (d, 2H, \(J = 8.0\) Hz, Ph), 6.50 (d, 2H, \(J = 8.0\) Hz, Ph), 6.04 (s, 1H, benzyl-H), 3.07 (s, 12H, 2CH\(_3\)), 0.98 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta\) = 196.0, 188.5, 154.1, 136.6, 128.3, 115.3, 114.3, 90.1, 50.9, 45.5, 42.1, 31.6, 30.7, 29.7, 11.7; LC/MS (ESI): 507 [M]+; Anal. for C\(_{25}\)H\(_{35}\)N\(_3\)O\(_6\): calcd: C, 63.41; H, 7.45; N, 8.87; Found: C, 63.40; H, 7.43; N, 8.85.

Table 3 Tandem Aldol-Michael reactions of barbituric acid 1a,b and dimedone 2 with aldehydes 3 in aqueous diethylamine medium\(^\text{a}\)

| # | R\(_1\) | R\(_2\) | yield (%)\(^\text{b}\) |
|---|---|---|---|
| 1 | 4a | Ph | 98 |
| 2 | 4b | p-CH\(_3\)Ph | 97 |
| 3 | 4c | p-CIPh | 97 |
| 4 | 4d | p-BrPh | 95 |
| 5 | 4e | m-BrPh | 93 |
| 6 | 4f | p-Ch\(_2\)OPh | 92 |
| 7 | 4g | o-NO\(_2\)Ph | 93 |
| 8 | 4h | 2,4-Cl\(_2\)Ph | 90 |
| 9 | 4i | 2,6-Cl\(_2\)Ph | 89 |
| 10 | 4j | 2-Naphthaldehyde | 94 |
| 11 | 4k | p-HO-Ph | 91 |
| 12 | 4l | Ph | 93 |
| 13 | 4m | p-CH\(_3\)Ph | 91 |
| 14 | 4n | p-CIPh | 90 |
| 15 | 4o | p-BrPh | 89 |
| 16 | 4p | 2-Naphthaldehyde | 90 |

\(^\text{a}\)All reactions were carried out with barbituric acid derivatives 1a,b (1.5 mmol), dimedone 2 (1.5 mmol) aldehydes 3 (1.5 mmol) and diethylamine (1.5 mmol) in water (1.5 mL) for the specified time. \(^\text{b}\)Yield of isolated product 4a-p.

5-((2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(phenyl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (4l)

4l was prepared from barbituric acid 1b, dimedone 2 and benzaldehyde 3 according to the general procedure.
(GP1) yielding a white solid material (598 mg, 1.39 mmol, 93%). m.p: 215°C; IR (KBr, cm\(^{-1}\)): 3027, 2948, 2867, 2156, 1683, 1593, 1451, 1374, 1291, 1257, 1141.\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 12.26 (s, 1H, OH), 9.31 (brs, 2H, NH), 7.12 (m, 5H, Ph), 5.52 (s, 1H, benzyl-H), 2.99 (q, 4H, J = 7.3 Hz, CH\(_2\)CH\(_3\)), 2.45 (d, 4H, J = 5.1 Hz, CH\(_2\)), 1.24 (t, 6H, J = 7.3 Hz, CH\(_3\)CH\(_2\)), 1.09 (s, 3H, CH\(_3\)), 1.03 (s, 3H, CH\(_3\)) \(\left(^{13}\right)\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 198.5, 180.8, 152.5, 142.5, 128.0, 126.7, 125.1, 116.3, 90.9, 51.4, 45.9, 42.2, 33.0, 28.4, 27.6, 11.3; LC/MS (ESI): 463 [M]+; Anal. for C\(_{23}\)H\(_{30}\)ClN\(_3\)O\(_5\); calcd: C, 59.54; H, 6.51; Cl, 7.60; N, 9.02.

5-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(p-tolyl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (4n) 4n was prepared from barbituric acid 1a, dimedone 2 and tolualdehyde 3 according to the general procedure (GP1) yielding a white solid material (604 mg, 1.36 mmol, 91%). m.p: 213°C; IR (KBr, cm\(^{-1}\)): 3150, 2955, 2867, 1690, 1592, 1508, 1375, 1256, 1232, 1167; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 13.31 (s, 1H, OH), 8.83 (brs, 2H, NH), 7.27 (d, 2H, J = 8.0 Hz, Ph), 7.00 (d, 2H, J = 8.0 Hz, Ph), 5.88 (s, 1H, benzyl-H), 2.83 (q, 4H, J = 7.3 Hz, CH\(_2\)CH\(_3\)), 2.31 (d, 4H, J = 5.1 Hz, CH\(_2\)), 2.23 (s, 3H, CH\(_3\)), 1.19 (t, 6H, J = 7.3 Hz, CH\(_3\)CH\(_2\)), 1.04 (s, 3H, CH\(_3\)), 1.02 (s, 3H, CH\(_3\)) \(\left(^{13}\right)\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 198.5, 180.8, 152.5, 141.0, 134.8, 131.0, 129.5, 128.3, 115.3, 91.1, 47.1, 42.7, 31.6, 31.5, 29.1, 28.2, 27.8, 11.3; LC/MS (ESI): 463 [M]+; Anal. for C\(_{23}\)H\(_{30}\)ClN\(_3\)O\(_5\); calcd: C, 54.35; H, 5.96; Cl, 7.60; Br, 15.69; N, 9.50.

5-(4-Chlorophenyl)(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (4o) 4o was prepared from barbituric acid 1a, dimedone 2 and p-chlorobenzaldehyde 3 according to the general procedure (GP1) yielding an oily product (625 mg, 1.35 mmol, 90%). IR (KBr, cm\(^{-1}\)): 3049, 2954, 2865, 2499, 1738, 1699, 1590, 1483, 1375, 1292, 1258, 1225, 1205; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 13.32 (s, 1H, OH), 8.83 (brs, 2H, NH), 7.27 (d, 2H, J = 8.0 Hz, Ph), 7.00 (d, 2H, J = 8.0 Hz, Ph), 5.89 (s, 1H, benzyl-H), 2.88 (q, 4H, J = 7.3 Hz, CH\(_2\)CH\(_3\)), 2.31 (d, 4H, J = 5.1 Hz, CH\(_2\)), 1.19 (t, 6H, J = 7.3 Hz, CH\(_2\)CH\(_3\)), 1.09 (s, 3H, CH\(_3\)), 1.03 (s, 3H, CH\(_3\)) \(\left(^{13}\right)\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 198.5, 180.8, 152.5, 140.5, 134.8, 131.0, 129.5, 128.3, 115.3, 91.1, 47.1, 42.7, 31.6, 31.5, 29.1, 28.2, 27.8, 11.3; LC/MS (ESI): 463 [M]+; Anal. for C\(_{23}\)H\(_{30}\)BrN\(_3\)O\(_5\); calcd: C, 59.54; H, 6.52; Cl, 7.64; N, 9.06; Found: C, 59.57; H, 6.51; Cl, 7.60; N, 9.02.

5-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(naphthalen-2-yl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (4p) 4p was prepared from barbituric acid 1a, dimedone 2 and 2-naphthaldehyde according to the general procedure (GP1) yielding an oily product (646 mg, 1.35 mmol, 90%). IR (KBr, cm\(^{-1}\)): 3049, 2948, 2863, 2725, 1685, 1594, 1508, 1371, 1252, 1216; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 14.25 (s, 1H, OH), 7.46-7.22 (m, 7H, naphthyl), 6.21 (s, 1H, H2O/NHEt2).
benzyl-H), 3.27 (s, 6H, 2CH3), 3.25 (s, 6H, 2CH3), 3.14 (q, 4H, J = 7.3 Hz, CH2CH3), 2.41 (q, 4H, J = 5.1 Hz, CH2), 2.23 (s, 2H, CH2), 1.37 (t, 6H, J = 7.3 Hz, CH2CH3), 1.07 (s, 3H, CH3), 1.01 (s, 3H, CH3); 13C NMR (100 MHz, CDCl3); δ = 199.1, 180.5, 165.5, 164.2, 154.2, 149.7, 136.8, 131.5, 129.9, 126.5, 124.2, 115.5, 114.7, 89.9, 50.9, 45.5, 41.7, 31.3, 30.7, 28.2, 11.3; LC/MS (ESI): 479 [M]+; Anal. for C27H33N3O5; calcld: C, 67.62; H, 6.94; N, 8.76; Found: C, 67.65; H, 6.96; N, 8.80.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
AB proposed the subject, designed the study. AMA carried out the synthesis and subsequent sorption on sodium dodecylsulfate/alumina and aluminum hydroxide for fluorescent analysis. Anal. Sci 2002, 18:1267–1268.

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