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Substrate-controlled selectivity switch in a three-component reaction: sequential synthesis of spiro-oxazolidinedione-cyclopentenones and hydroxy enamino-barbiturates in water†

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An efficient eco-friendly catalyst-free three-component domino multicyclization for the synthesis of new spirobicyclic oxazolidinedione containing cyclopentenone moieties has been established by mixing amines, β -dicarbonyl compounds and *N,N'*-dimethylalloxan in water at room temperature. This domino process involves multiple reactions such as enamination/aldol-like reaction/Stork enamine annulation/intramolecular cyclization under mild conditions.

Introduction

The efficient assembly of complex heterocyclic compounds with chemical and biomedical importance is a challenging and hot topic in modern organic chemistry.^{1,2} Among these heterocycles, the structurally diverse oxazolidinedione is a versatile component of many biologically active compounds. A great number of oxazolidinedione-containing pharmaceuticals are being used for therapeutic and clinical utilization. As representative compounds, paramethadione (Paradione®), and trimethadione (Tridione®) are two anticonvulsant medications in the oxazolidinedione family used commonly to treat seizures and epileptic conditions.³ It has also been reported recently for their bioactivities such as hypoglycaemic and hypolipidemic agents,⁴ muscarinic agonists,⁵ anticonvulsants⁶ and insulin sensitizers with antidiabetic activities⁷ elastase inhibitor,⁸ serine protease inhibitor,⁹ mineralocorticoid receptor (MR) antagonist,¹⁰ and anti-cancer.¹¹ Furthermore, spiro-fused oxazolidinediones were frequently reported to possess aldose reductase inhibitory properties.¹²

Spirocyclic five-membered carbocycles are not only the key structural motifs in a number of natural products but also serve as privileged building blocks to a variety of biologically significant class of compounds.¹³ For instance, amino cyclopentenones are particularly useful building blocks in the asymmetric synthesis of prostaglandins, prostanoid derivatives, jasmonates and other bioactive molecules.¹⁴ Although the synthesis of 2-cyclopenten-1-ones as a challenging area in methodological studies is accomplished in a variety synthetic routes, including more classical methods such as the aldol reaction,¹⁵ as well as

newer methods such as the Nazarov cyclization reaction,¹⁶ Saegusa–Ito oxidation of cyclopentanones, ring-closing metathesis, oxidation of cyclic allylic alcohols, and the Pauson–Khand reaction,¹⁷ to the best of our knowledge, there are only few reports¹⁸ on the synthesis of 3-cyclopenten-1-ones especially their spiro-fused derivatives (Fig. 1).

The “green chemistry” movement calls for redesigning new chemical processes and making reaction conditions safer that can potentially provide advantages for chemical syntheses in terms of waste treatment, energy and resource efficiency, product selectivity and environmental safety.¹⁹ Over the last decade multicomponent cascade reactions, particularly those performed in water as a cheap, non-flammable, nontoxic and environmentally friendly solvent, has witnessed considerable growth and development as a powerful tool in organic synthesis because of their expedient building up of molecular complexity and diversity, operational simplicity, convergence, atom economy, bond-forming efficiency and other suitable features from the point of view of green chemistry.^{20,21}

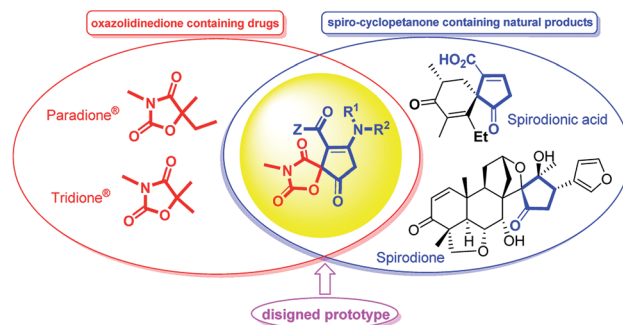


Fig. 1 Some biologically important oxazolidinedione- and cyclopentane-containing drugs and designed cyclopentenone-fused spiro-oxazolidinediones hybrid prototype.

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In principle, alloxans (pyrimidine-2,4,5,6(1*H*,3*H*)-tetrone)s should be regarded as suitable reaction partners for aldol-like reaction of enamines by virtue of the outstanding electrophilicity of the C=O bond on the 5-position, and a series of biological important barbiturate derivatives can be assembled conveniently. Considering the efficiency as well as green chemistry aspects of aqueous-phase multicomponent reactions, recently our group have introduced a series of convenient methods with alloxans to provide biologically-interesting pyrimidine-containing heterocyclic compounds in water.^{22a-d} It has been reported that when a mixture of alloxan derivatives and β -enaminoester derived *in situ* from the reaction of amines and acetylenic esters was stirred in water, the hydroxy enamino-barbiturates^{22c} (Scheme 1, eqn (1)) and oxospirobicyclic butenolidobarbiturates^{22d} (Scheme 1, eqn (2)) were produced. Inspired by the previous works as well as our continuous interests on the development of β -enamino-carbonyl-based synthesis of pharmaceutically important heterocycles, during this project, we found that when β -enaminoester employed in the above literatures were produced by reaction of amines and β -dicarbonyl compounds, the reaction occurred in another direction to form cyclopentenone-fused spiro oxazolidinediones in water that are important scaffolds for organic synthesis and drug design in pharmaceutical sciences (Scheme 1, eqn (3)). Surprisingly, no report has appeared for the synthesis of cyclopentenone-fused spiro oxazolidinediones. Encouraged by this initial result, we then made many efforts on optimizing reaction conditions.

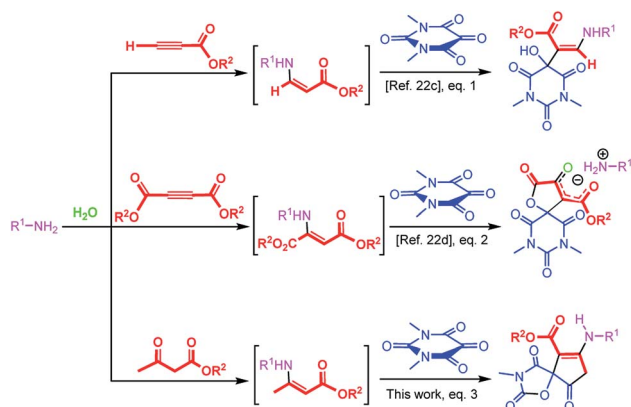
Results and discussion

In optimization of the reaction conditions, first we focused on the efficient preparation of β -enaminoester or β -enaminones **5** from amines **1** and β -dicarbonyl compounds **2**. Although a number of methods have been developed for the preparation of β -enamino-carbonyl compounds, considering the phrase, “the best solvent is no solvent and if a solvent (diluent) is needed then water is preferred” as clearly quoted by Sheldon in a review article,²³ we chose solventless catalyst-free reaction

conditions for the preparation of β -enaminoester and β -enaminones according to a previously reported procedure.²⁴ At first the primary or secondary amine components reacted with β -dicarbonyl compounds without using any solvent or catalyst at room temperature for appropriate time to give the corresponding β -enamino-carbonyl compounds. The reaction time required for the enamination step are given in Table 1. Subsequently, an aqueous solution of *N,N*-dimethylalloxan was added and the resulting mixture was stirred at room temperature for additional 1 h. The reactions were completed in all cases within only one hour and the products **4a-s** were precipitated in the reaction mixture. The results are summarized in Table 1. ¹H NMR and ¹³C NMR spectra of the crude products clearly indicated the formation of **4**. It is also noteworthy to mention that this is the first report on the synthesis of 1-oxa-3-aza-spiro[4.4]non-6-enes that are important scaffolds for organic synthesis and drug design in pharmaceutical sciences.

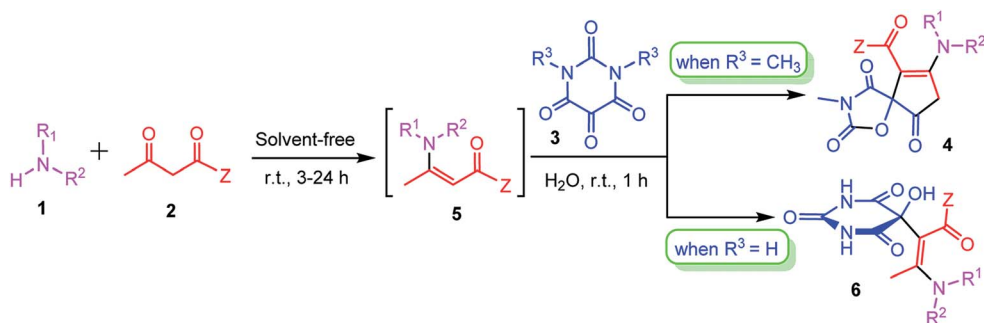
Compounds **4a-s** are stable colorless solids whose structures were established by their analytical as well as spectral studies including FT-IR, ¹H NMR, ¹³C NMR, and elemental analysis. For example, in the ¹H NMR spectrum of **4a**, the protons from O=C-CH₃ and two different NCH₃ groups gave three singlets at δ_{H} 2.27, 3.14 and 3.16 ppm. An AB-quartet resonance was assigned (3.55 and 3.90 ppm, ²J_{HH} 19.5 Hz) for the methylene of oxazolidinedione moiety. The NH group as a singlet (δ_{H} 5.84 ppm) was identified easily. The ¹³C{¹H}-NMR spectrum of **4a** showed 11 distinct resonances, which confirmed the proposed structure. The structural assignments made on the basis of the NMR spectra of compounds **4a** was supported by the observed carbonyl frequency at 1853 cm⁻¹ in FT-IR spectrum which is characteristic for oxazolidinedione ring.²⁵

Under the optimized reaction conditions, a variety of primary and secondary aliphatic amines such as methylamine, ethylamine, *n*-propylamine, iso-butylamine, allylamine, propargyl amine, iso-propyl amine, piperidine, morpholine and thiomorpholine were employed and the reaction proceeded smoothly to give the corresponding spiro-oxazolidinedione-cyclopentenones **4a-s** in moderate to good yields. Because the lower nucleophilicity and also lower hydrophilicity of aromatic amines (aniline derivatives) than that of aliphatic amines, unfortunately, our attempts to carry out this reaction under the same reaction conditions by using aromatic amines were unsuccessful and the reaction led to intractable mixture. Only with 4-hydroxyaniline (aniline bearing an strong electron-donating hydrophilic group) the corresponding 1-oxa-3-aza-spiro[4.4]non-6-enes **4l** was obtained in 35% yield (Table 1, entry 12). Moreover, to extend the scope of this reaction with respect to β -dicarbonyl compounds, three alkyl acetoacetates and one 1,3-diketone were surveyed. The results show that the reaction is quite general with methyl acetoacetate, ethyl acetoacetate, *tert*-butyl acetoacetate, and acetylacetone affording **4**, but failed to furnish the expected products with 1-phenylbutane-1,3-dione and ethyl 3-oxopentanoate. During further substrate screening, when the substrate combination was switched from *N,N*-dimethylalloxan to alloxan using the optimized conditions, to our surprise the expected products **4**



Scheme 1 Recently reported β -enaminoester-based MCRs of *N,N*-dimethylalloxan in water.

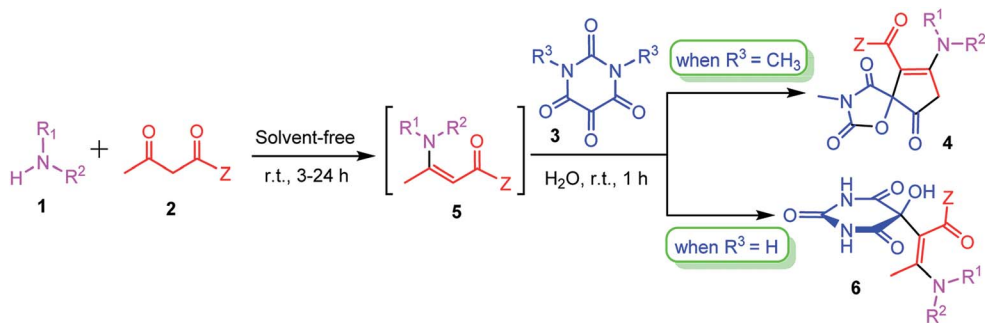


Table 1 One-pot synthesis of spiro-oxazolidinedione-cyclopentenones and hydroxy enamino-barbiturates^a

Entry	Amine	Z	Time (h)	Product	Yield ^b (%)
1		CH ₃	3		75
2		CH ₃	3		67
3		CH ₃	3		65
4		CH ₃	3		65
5		CH ₃	3		59
6		CH ₃	3		60
7		OCH ₃	3		78
8		OCH ₂ CH ₃	3		70
9		OCH ₃	3		72



Table 1 (Contd.)



Entry	Amine	Z	Time (h)	Product	Yield ^b (%)
10		OCH ₂ CH ₃	3		65
11		OCH ₂ CH ₃	3		60
12		OCH ₂ CH ₃	3		35
13		OC(CH ₃) ₃	3		55
14		OCH ₃	24		58
15		OCH ₂ CH ₃	24		51
16		OCH ₃	16		58
17		OCH ₂ CH ₃	16		60

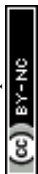
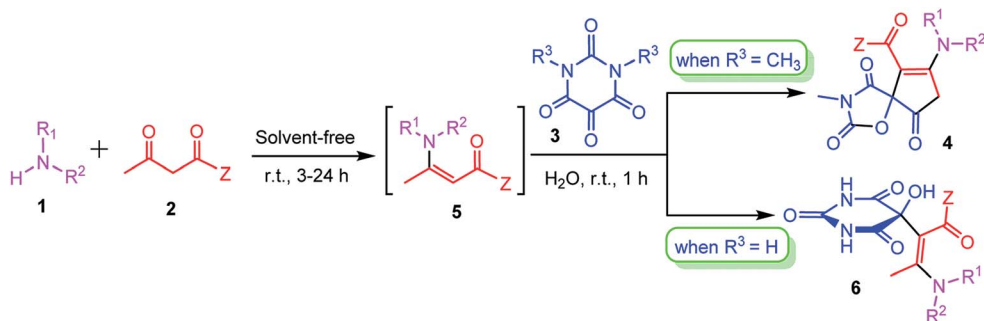


Table 1 (Contd.)



Entry	Amine	Z	Time (h)	Product	Yield ^b (%)
18		OCH ₃	24		64
19		OCH ₂ CH ₃	24		61
20		CH ₃	3		87
21		CH ₃	3		83
22		OCH ₂ CH ₃	3		75
23		OCH ₂ CH ₃	3		68

^a Reaction conditions: a solution of alloxan derivative 3 (1 mmol) in 3 mL water was added to the mixture of *in situ*-generated β -enaminocarbonyl compound from amine 1 (1 mmol) and β -dicarbonyl compound 2 (1 mmol) under solvent-free conditions at 25 °C (3–24 h) and the resulting mixture was stirred at room temperature for additional 1 h. The product 4 or 6 was separated by filtration. ^b Isolated yield.

was not obtained and hydroxy enaminobarbiturates 6 was gained instead as the product (Table 1, entries 20–23).

As an economic and efficient protocol, the scale-up and operational simplicity of the three-component reaction have great practical significance for the preparation of spiro-

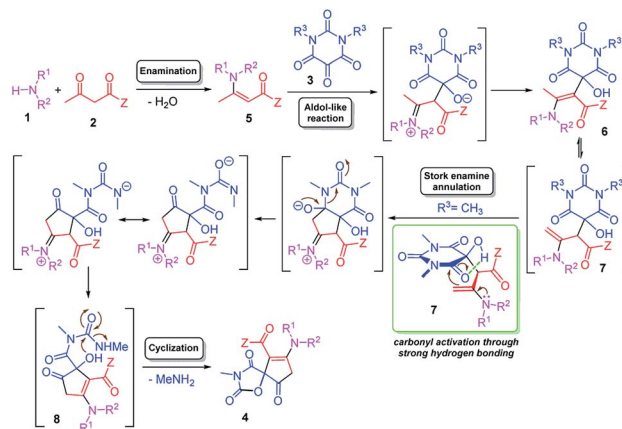
oxazolidinedione-cyclopentenones in the academic laboratory, and even in industry. Thus, the different scale reactions of methyl amine, acetylaceton with *N,N'*-dimethylalloxan were carried out under the optimized reaction conditions. As shown in Scheme 2, the high-purity spiro-oxazolidinedione-



cyclopentenone **4a** can be simply obtained by filtration and washing with diethyl ether. This straightforward protocol followed environmentally-friendly GAP chemistry (group-assistant-purification chemistry), which avoids conventional purification procedures such as organic solvent extraction, silica gel column chromatography, and recrystallization.²⁶ This is in conformity with the first of the principles of green chemistry, which is that it is better to prevent waste rather than to treat or clean up waste after it is formed.

Since the reusability of reaction medium is of great importance from the views of industry, economy and green chemistry, we examined the reusability of water after extraction of reaction residue with diethyl ether. We found that the reaction medium (water) after this extractive workup could be reused at least four times without significant loss of yield.

A possible mechanism was proposed as shown in Scheme 3. The initial step could be the dehydrative condensation of the amine **1** and 1,3-dicarbonyl compound **2** which affords the enaminone **5**. Subsequently, a aldol-type addition of the enaminone **5** to the central carbonyl group of the alloxan derivative **3** occurs to generate the key iminium-oxyanion intermediate, which undergoes an iminium-enamine tautomerization and proton transfer to afford enamino hydroxybarbiturates **6** and **7** in an equilibrium. Now, the methyl group in **6** has been activated to enaminomethylene group in **7** by the isomerization. Then, intramolecular Stork enamine annulation between enaminomethylene moiety and imidic carbonyl group²⁷ of **7** followed by ring opening of barbiturate moiety, iminium-enamine tautomerization and proton transfer afford the hydroxyl-cyclopentenone **8** and the latter undergoes intramolecular cyclization with concomitant methyl amine elimination to give the spiro-oxazolidinedione-cyclopentenone **4** (Scheme 3). The most exciting feature of this protocol is its mechanism that we have postulated here involving the unusual ring opening of a barbiturate moiety. This is probably because of the imidic carbonyl can be activated through the strong envelop-like five-membered hydrogen bonding with the vicinal hydroxyl group in intermediate **7**. On the other hand, the leaving group which is similar to the conjugate base of *N*-methylurea can be a very good leaving group because it has two stable resonance structures.



Scheme 3 Proposed reaction mechanism.

Conclusions

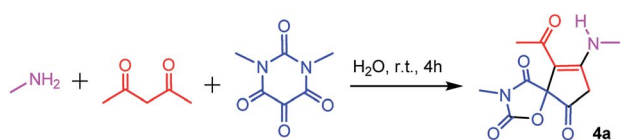
In summary, we have developed an eco-friendly efficient strategy for the synthesis of spiro-oxazolidinedione-cyclopentenones and hydroxy enamino-barbiturates from readily available primary or secondary amines, β -enamino-carbonyl compounds and alloxan derivatives under catalyst-free conditions in water. At least four distinct reactions (enamination, aldol-type addition, Stork enamine annulation and cyclization) take place in this aqueous one-pot three-component process at room temperature to produce to produce the drug-like functionalized spiro-oxazolidinedione-cyclopentenones. All these reactions occur in an ordered manner to produce the final product with concomitant creation of four new bonds (two C-C, one C-N and one C-O) and two new rings.

Experimental

General remarks

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using an elemental vario EL III instrument. FT-IR Spectra were recorded on a Bruker Equinox-55 spectrometer. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively, with CDCl₃ as solvent and calibrated using residual undeuterated solvent as an internal reference. Data for ¹H NMR were presented as following: chemical shifts (δ , ppm), integration, multiplicity, coupling constant (Hz) and assignment of protons. The chemical shifts of resonances found were reported for ¹³C NMR spectra. Analytical TLC was carried out on pre-coated plates (Merck silica gel 60, F254) and visualized with UV light. All chemical reagents were obtained from Aldrich, Merck, Fluka or Acros and were used without further purification.

Typical procedure for the synthesis of 4 or 6. In a screw-capped test tube, a mixture of the amine (1 mmol) and the β -dicarbonyl compound (1 mmol) was stirred with a magnetic stirring bar under solvent-free conditions at room temperature



	Purification	Yield
0.5 mmol	Filtration and washing by Et ₂ O	75%, 0.095 g
5 mmol	Filtration and washing by Et ₂ O	73%, 0.920 g
10 mmol	Filtration and washing by Et ₂ O	69%, 1.740 g
20 mmol	Filtration and washing by Et ₂ O	67%, 3.379 g

Scheme 2 Gram-scale synthesis of **4a**.



(25 °C) for the time specified in Table 1 (3–24 h). Then, a solution of alloxan derivative (1 mmol) in 3 mL water was added to the reaction mixture and the resulting mixture was stirred at room temperature for additional 1 h until the completion of the reaction as evidenced by TLC monitoring (hexane/EtOAc 4 : 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 **4** or **6** as a white powder. The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.

9-Acetyl-3-methyl-8-(methylamino)-1-oxa-3-aza-spiro[4.4]non-8-ene-2,4,6-trione (4a). White powder (0.190 g, 75%); mp 131–133 °C (dec.); IR (KBr) (ν_{\max} , cm^{-1}): 3470 (NH), 1853, 1735, 1703 and 1675 (C=O); ^1H NMR (CDCl_3 , 300.1 MHz): δ_{H} 2.27 (3H, s, O=C-CH₃), 3.14 (3H, s, NCH₃), 3.16 (3H, s, NCH₃), 3.55 and 3.90 (2H, AB system, $^2J_{\text{HH}}$ 19.5 Hz, O=C-CH₂), 5.84 (1H, s, NH); ^{13}C NMR (CDCl_3 , 75.5 MHz): δ_{C} 196.6, 169.4, 167.1, 153.4, 151.7, 102.7, 82.4, 34.3, 31.7, 28.3, 26.8; anal. calcd for C₁₁H₁₂N₂O₅ (252.23): C 52.38, H 4.80, N 11.11%; found: C 52.51, H 4.68, N 11.02%.

9-Acetyl-8-(ethylamino)-3-methyl-1-oxa-3-aza-spiro[4.4]non-8-ene-2,4,6-trione (4b). White powder (0.179 g, 67%); mp 137–139 °C (dec.); IR (KBr) (ν_{\max} , cm^{-1}): 3457 (NH), 1834, 1747, 1734 and 1677 (C=O), 1591 (C=C); ^1H NMR (CDCl_3 , 300.1 MHz): δ_{H} 1.27 (3H, t, $^3J_{\text{HH}} = 7.2$ Hz, CH₂CH₃), 2.29 (3H, s, O=C-CH₃), 3.18 (3H, s, NCH₃), 3.69 (2H, m, CH₂CH₃), 3.54 and 3.92 (2H, AB system, $^2J_{\text{HH}}$ 19.5 Hz, O=C-CH₂), 5.90 (1H, s, NH); ^{13}C NMR (CDCl_3 , 75.5 MHz): δ_{C} 196.7, 169.5, 167.1, 153.9, 150.7, 102.3, 82.4, 36.9, 34.5, 31.8, 26.7, 11.7; anal. calcd for C₁₂H₁₄N₂O₅ (266.25): C 54.13, H 5.30, N 10.52%; found: C 53.85, H 5.25, N 10.54%.

9-Acetyl-3-methyl-8-(propylamino)-1-oxa-3-aza-spiro[4.4]non-8-ene-2,4,6-trione (4c). White powder (0.182 g, 65%); mp 138–140 °C (dec.); IR (KBr) (ν_{\max} , cm^{-1}): 3479 (NH), 1832, 1754, 1739 and 1678 (C=O), 1592 (C=C). ^1H NMR (CDCl_3 , 300.1 MHz): δ_{H} 0.83 (3H, t, $^3J_{\text{HH}} = 7.30$ Hz, CH₂CH₂CH₃), 1.55 (2H, sex., CH₂-CH₂CH₃), 2.19 (3H, s, O=C-CH₃), 2.96 (3H, s, NCH₃), 3.58 (2H, m, NH-CH₂), 3.42 and 3.83 (2H, AB system, $^2J_{\text{HH}}$ 19.5 Hz, O=C-CH₂), 6.18 (1H, s, NH); ^{13}C NMR (CDCl_3 , 75.5 MHz): δ_{C} 196.8, 170.1, 168.0, 154.6, 151.0, 102.9, 82.7, 42.5, 34.2, 31.5, 26.4, 19.4, 10.8; anal. calcd for C₁₃H₁₆N₂O₅ (280.28): C 55.71, H 5.75, N 10.00%; found: C 55.56, H 5.68, N 9.94%.

9-Acetyl-8-(isobutylamino)-3-methyl-1-oxa-3-azaspiro[4.4]non-8-ene-2,4,6-trione (4d). White powder (0.192 g, 65%); mp 178–180 °C (dec.); IR (KBr) (ν_{\max} , cm^{-1}): 3476 (NH), 1829, 1754, 1737 and 1680 (C=O), 1603 (C=C); ^1H NMR (CDCl_3 , 300.1 MHz): δ_{H} 0.93 and 0.96 (6H, d, $^3J_{\text{HH}}$ 6.8 Hz, CHMe₂), 2.12 (1H, m, CH), 2.27 (3H, s, O=C-CH₃), 3.16 (3H, s, NCH₃), 3.44 (2H, m, NHCH₂), 3.55 and 3.93 (2H, AB system, $^2J_{\text{HH}}$ 19.5 Hz, O=C-CH₂), 5.84 (1H, s, NH); ^{13}C NMR (CDCl_3 , 75.5 MHz): δ_{C} 196.6, 169.6, 167.7, 154.0, 151.4, 102.7, 82.4, 49.0, 34.3, 31.8, 26.7, 26.1, 20.0, 19.8; anal. calcd for C₁₄H₁₈N₂O₅ (294.31): C 57.14, H 6.16, N 9.52%; found: C 56.98, H 6.13, N 9.45%.

9-Acetyl-8-(allylamino)-3-methyl-1-oxa-3-aza-spiro[4.4]non-8-ene-2,4,6-trione (4e). White powder (0.165 g, 59%); mp 140–143 °C (dec.); IR (KBr) (ν_{\max} , cm^{-1}): 3467 (NH), 1834, 1753, 1737 and 1678 (C=O), 1650 and 1589 (C=C); ^1H NMR (CDCl_3 ,

300.1 MHz): δ_{H} 2.24 (3H, s, O=C-CH₃), 3.16 (3H, s, NCH₃), 3.56 and 3.93 (2H, d of AB-system, $^2J_{\text{HH}}$ 19.5 Hz, $^4J_{\text{HH}}$ 1.5 Hz, O=C-CH₂), 4.22–4.27 (2H, m, NHCH₂), 5.24 and 5.29 (2H, d, $^3J_{\text{HH(Trans)}}$ 17.2 Hz, $^3J_{\text{HH(Cis)}}$ 10.4 Hz, =CH₂), 5.67–5.80 (1H, m, =CH), 5.83 (1H, s, NH); ^{13}C NMR (CDCl_3 , 75.5 MHz): δ_{C} 196.7, 169.6, 167.9, 153.8, 150.4, 128.4, 118.6, 103.3, 82.4, 43.9, 34.4, 31.8, 26.8; anal. calcd for C₁₃H₁₄N₂O₅ (278.26): C 56.11, H 5.07, N 10.07%; found: C 55.79, H 4.99, N 10.18%.

9-Acetyl-3-methyl-8-(prop-2-yn-1-ylamino)-1-oxa-3-aza-spiro[4.4]non-8-ene-2,4,6-trione (4f). White powder (0.166 g, 60%); mp 134–136 °C (dec.); IR (KBr) (ν_{\max} , cm^{-1}): 3459 (NH), 3315 ($\equiv\text{C-H}$), 1837, 1748, 1684 (C=O), 1597 (C=C); ^1H NMR (CDCl_3 , 300.1 MHz): δ_{H} 2.28 (3H, s, O=C-CH₃), 2.35 (1H, t, $^4J_{\text{HH}}$ 2.5 Hz, $\equiv\text{CH}$), 3.15 (3H, s, NCH₃), 3.58 and 3.92 (2H, AB-system, $^2J_{\text{HH}}$ 19.6 Hz, O=C-CH₂), 4.32 and 4.45 (2H, d of AB-system, $^2J_{\text{HH}}$ 17.6 Hz, $^4J_{\text{HH}}$ 2.5 Hz, HC $\equiv\text{C-CH}_2$), 6.04 (1H, s, NH); ^{13}C NMR (CDCl_3 , 75.5 MHz): δ_{C} 196.6, 169.2, 166.4, 153.7, 149.1, 103.9, 82.2, 74.3, 74.1, 34.3, 31.8, 31.1, 26.8; anal. calcd for C₁₃H₁₂N₂O₅ (276.25): C 56.52, H 4.38, N 10.14%; found: C 56.35, H 4.40, N 10.17%.

Methyl 3-methyl-7-(methylamino)-2,4,9-trioxo-1-oxa-3-aza-spiro[4.4]non-6-ene-6-carboxylate (4g). White powder (0.210 g, 78%); mp 199–202 °C (dec.); IR (KBr) (ν_{\max} , cm^{-1}): 3390 (NH), 1836, 1745, 1743 and 1699, 1638 (C=O); ^1H NMR (CDCl_3 , 300.1 MHz): δ_{H} 3.13 (3H, s, NCH₃), 3.16 (3H, s, NCH₃), 3.73 (3H, s, OCH₃), 3.55 and 3.90 (2H, d of AB-system, $^2J_{\text{HH}}$ 19.3 Hz, $^4J_{\text{HH}}$ 1.8 Hz, O=C-CH₂), 5.43 (1H, t, $^3J_{\text{HH}}$ 1.8 Hz, NH); ^{13}C NMR (CDCl_3 , 75.5 MHz): δ_{C} 169.5, 166.8, 166.5, 153.9, 152.4, 95.4, 82.4, 51.5, 33.5, 28.3, 26.8; anal. calcd for C₁₁H₁₂N₂O₆ (268.23): C 49.26, H 4.51, N 10.44%; found: C 49.47, H 4.57, N 10.37%.

Ethyl 3-methyl-7-(methylamino)-2,4,9-trioxo-1-oxa-3-aza-spiro[4.4]non-6-ene-6-carboxylate (4h). White powder (0.198 g, 70%); mp 139–141 °C (dec.); IR (KBr) (ν_{\max} , cm^{-1}): 3389 (NH), 1828, 1748, 1747 and 1698, 1651 (C=O); ^1H NMR (CDCl_3 , 300.1 MHz): δ_{H} 1.29 (3H, t, $^3J_{\text{HH}}$ 7.1 Hz, OCH₂CH₃), 3.13 (3H, s, NCH₃), 3.16 (3H, s, NCH₃), 3.55 and 3.90 (2H, d of AB-system, $^2J_{\text{HH}}$ 19.2 Hz, $^4J_{\text{HH}}$ 1.7 Hz, O=C-CH₂), 4.19 (2H, q, $^3J_{\text{HH}}$ 7.1 Hz, OCH₂CH₃), 5.43 (1H, t, $^3J_{\text{HH}}$ 1.7 Hz, NH); ^{13}C NMR (CDCl_3 , 75.5 MHz): δ_{C} 169.5, 166.8, 166.1, 153.9, 152.1, 95.9, 82.5, 60.3, 33.5, 28.2, 26.8, 14.3; anal. calcd for C₁₂H₁₄N₂O₆ (282.25): C 51.07, H 5.00, N 9.93%; found: C 50.78, H 5.04, N 10.02%.

Methyl 7-(ethylamino)-3-methyl-2,4,9-trioxo-1-oxa-3-aza-spiro[4.4]non-6-ene-6-carboxylate (4i). White powder (0.204 g, 72%); mp 139–141 °C (dec.); IR (KBr) (ν_{\max} , cm^{-1}): 3464 (NH), 1835, 1738, 1708 and 1629 (C=O), ^1H NMR (CDCl_3 , 300.1 MHz): δ_{H} 1.23 (3H, t, $^3J_{\text{HH}}$ 7.2 Hz, OCH₂CH₃), 3.16 (3H, s, NCH₃), 3.66 (2H, ABX₃-system, NCH₂CH₃), 3.73 (3H, s, OCH₃), 3.53 and 3.90 (2H, d of AB-system, $^2J_{\text{HH}}$ 19.3 Hz, $^4J_{\text{HH}}$ 1.8 Hz, O=C-CH₂), 5.46 (1H, t, $^4J_{\text{HH}}$ 1.8 Hz, NH); ^{13}C NMR (CDCl_3 , 75.5 MHz): δ_{C} 169.5, 166.6, 153.9, 151.3, 95.0, 82.4, 51.4, 36.9, 33.7, 26.7, 11.6; anal. calcd for C₁₂H₁₄N₂O₆ (282.25): C 51.07, H 5.00, N 9.93%; found: C 50.79, H 4.94, N 9.88%.

Ethyl 7-(ethylamino)-3-methyl-2,4,9-trioxo-1-oxa-3-aza-spiro[4.4]non-6-ene-6-carboxylate (4j). White powder (0.193 g, 65%); mp 89–91 °C (dec.); IR (KBr) (ν_{\max} , cm^{-1}): 3392 (NH), 1831, 1750, 1705, 1650 (C=O), ^1H NMR (CDCl_3 , 300.1 MHz): δ_{H} 1.24 (3H, t, $^3J_{\text{HH}}$ 7.3 Hz, NCH₂CH₃), 1.29 (3H, t, $^3J_{\text{HH}}$ 7.3 Hz, OCH₂CH₃), 3.17



(3H, s, NCH₃), 3.59 and 3.86 (2H, d of AB-system, ²J_{HH} 19.2 Hz, ⁴J_{HH} 1.8 Hz, O=C-CH₂), 3.62–3.71 (2H, ABX₃-system, NCH₂CH₃), 4.18 (2H, q, ³J_{HH} 7.3 Hz, OCH₂CH₃), 5.45 (1H, t, ⁴J_{HH} 1.8 Hz, NH); ¹³C NMR (CDCl₃, 75.5 MHz): δ_C 169.5, 166.6, 166.2, 153.9, 151.0, 95.4, 82.5, 60.3, 36.9, 33.6, 26.7, 14.3, 11.6; anal. calcd for C₁₃H₁₆N₂O₆ (296.28): C 52.70, H 5.44, N 9.46%; found: C 53.02, H 5.40, N 9.55%.

Ethyl 7-(isopropylamino)-3-methyl-2,4,9-trioxo-1-oxa-3-azaspiro[4.4]non-6-ene-6-carboxylate (4k). White powder (0.186 g, 60%); mp 175–177 °C (dec.); IR (KBr) (ν_{max}, cm⁻¹): 3366 (NH), 1821, 1755, 1705, 1660 (C=O), 1605 (C=C); ¹H NMR (CDCl₃, 300.1 MHz): δ_H 1.32–1.39 (9H, m, 3 CH₃ overlapping), 3.12 (3H, s, NCH₃), 3.02 and 3.33 (2H, AB-system, ²J_{HH} 17.9 Hz, O=C-CH₂), 3.79–3.82 (1H, m, CH), 4.28 (2H, q, ³J_{HH} 7.1 Hz, OCH₂CH₃), 9.36 (1H, d, ³J_{HH} 7.7 Hz, NH); ¹³C NMR (CDCl₃, 75.5 MHz): δ_C 184.1, 175.5, 170.9, 166.0, 154.7, 99.0, 85.4, 60.5, 47.5, 32.3, 26.5, 23.4, 23.3, 14.2; anal. calcd for C₁₄H₁₈N₂O₆ (310.31): C 54.19, H 5.85, N 9.03%; found: C 53.96, H 5.83, N 9.07%.

Ethyl 7-[(4-hydroxyphenyl)amino]-3-methyl-2,4,9-trioxo-1-oxa-3-aza-spiro[4.4]non-6-ene-6-carboxylate (4l). White powder (0.126 g, 35%); mp 196–200 °C (dec.); IR (KBr) (ν_{max}, cm⁻¹): 3398 (OH + NH), 1837, 1750, 1708 and 1641 (C=O), 1598 (C=C); ¹H NMR (CDCl₃, 300.1 MHz): δ_H 1.25 (3H, t, ³J_{HH} 7.1 Hz, OCH₂CH₃), 3.19 (3H, s, NCH₃), 3.68 and 4.05 (2H, d of AB-system, ²J_{HH} 19.3 Hz, ⁴J_{HH} 2.0 Hz, O=C-CH₂), 4.14 (2H, q, ³J_{HH} 7.1 Hz, OCH₂CH₃), 5.21 (1H, t, ⁴J_{HH} 1.8 Hz, NH), 6.60 (1H, brs, OH), 6.86 and 7.04 (4H, 2 d, ³J_{HH} 7.1 Hz, -C₆H₄); ¹³C NMR (CDCl₃, 75.5 MHz): 169.5, 167.0, 166.4, 157.3, 153.9, 153.2, 128.5, 124.5, 116.9, 97.7, 82.7, 60.4, 33.5, 26.8, 14.2; anal. calcd for C₁₇H₁₆N₂O₇ (360.31): C 56.67, H 4.48, N 7.77%; found: C 56.43, H 4.53, N 7.86%.

tert-Butyl 3-methyl-7-(methylamino)-2,4,9-trioxo-1-oxa-3-azaspiro[4.4]non-6-ene-6-carboxylate (4m). White powder (0.170 g, 55%); mp 183–186 °C (dec.); IR (KBr) (ν_{max}, cm⁻¹): 3436 (NH), 1834, 1759, 1746 and 1700 (C=O), 1644 (C=C); ¹H NMR (CDCl₃, 300.1 MHz): δ_H 1.49 (9H, s, C(CH₃)₃), 3.11 (3H, s, NCH₃), 3.16 (3H, s, NCH₃), 3.84 (2H, AB-system, ²J_{HH} 19.2 Hz, O=C-CH₂), 5.35 (1H, s, NH). ¹³C NMR (CDCl₃, 75.5 MHz): 169.6, 166.7, 165.4, 153.4, 150.3, 97.8, 82.6, 80.8, 33.4, 28.2, 26.8; anal. calcd for C₁₄H₁₈N₂O₆ (310.30): C 54.19, H 5.85, N 9.03%; found: C 53.98, H 5.90, N 8.95%.

Methyl 3-methyl-2,4,9-trioxo-7-piperidin-1-yl-1-oxa-3-azaspiro[4.4]non-6-ene-6-carboxylate (4n). White powder (0.187 g, 58%); mp 193–195 °C (dec.); IR (KBr) (ν_{max}, cm⁻¹): 1816, 1727, 1701, 1667 (C=O), 1592 (C=C); ¹H NMR (CDCl₃, 300.1 MHz): δ_H 1.79 (6H, m, CH₂CH₂CH₂), 3.01 and 3.24 (2H, AB-system, ²J_{HH} 16.6 Hz, O=C-CH₂), 3.12 (3H, s, NCH₃), 3.54 (4H, m, CH₂NCH₂), 3.82 (3H, s, OCH₃); ¹³C NMR (CDCl₃, 75.5 MHz): δ_C 185.7, 170.9, 170.3, 164.3, 154.4, 103.7, 85.4, 53.2, 51.5, 50.7, 35.7, 26.0, 25.9, 25.2, 23.0; anal. calcd for C₁₅H₁₈N₂O₆ (322.32): C 55.90, H 5.63, N 8.69%; found: C 56.17, H 5.60, N 8.76%.

Ethyl 3-methyl-2,4,9-trioxo-7-piperidin-1-yl-1-oxa-3-azaspiro[4.4]non-6-ene-6-carboxylate (4o). White powder (0.172 g, 51%); mp 115–117 °C (dec.); IR (KBr) (ν_{max}, cm⁻¹): 1820, 1742, 1711, 1678 (C=O), 1568 (C=C); ¹H NMR (CDCl₃, 300.1 MHz): δ_H 1.32 (3H, t, ³J_{HH} 7.1 Hz, OCH₂CH₃), 1.76 (6H, m, CH₂CH₂CH₂), 3.00 and 3.22 (2H, AB-system, ²J_{HH} 16.6 Hz, O=C-CH₂), 3.10 (3H, s, NCH₃), 3.53 (4H, m, CH₂NCH₂), 4.26 (2H, q, ³J_{HH} 7.1 Hz,

OCH₂CH₃); ¹³C NMR (CDCl₃, 75.5 MHz): δ_C 185.7, 170.7, 170.4, 164.2, 154.7, 103.2, 85.8, 60.9, 53.4, 51.0, 35.9, 26.4, 26.2, 25.6, 23.4, 14.2; anal. calcd for C₁₆H₂₀N₂O₆ (336.34): C 57.14, H 5.99, N 8.33%; found: C 56.88, H 6.08, N 8.28%.

Methyl 3-methyl-7-morpholin-4-yl-2,4,9-trioxo-1-oxa-3-azaspiro[4.4]non-6-ene-6-carboxylate (4p). White powder (0.188 g, 58%); mp 193–195 °C (dec.); IR (KBr) (ν_{max}, cm⁻¹): 1820, 1745, 1723, 1662 (C=O), 1576 (C=C); ¹H NMR (CDCl₃, 300.1 MHz): δ_H 3.04 and 3.24 (2H, AB-system, ²J_{HH} 16.7 Hz, O=C-CH₂), 3.12 (3H, s, NCH₃), 3.62–3.72 (4H, m, CH₂NCH₂), 3.81 (3H, s, OCH₃), 3.88 (4H, m, CH₂OCH₂); ¹³C NMR (CDCl₃, 75.5 MHz): δ_C 185.8, 171.4, 170.4, 163.8, 154.5, 103.1, 85.4, 66.4, 66.3, 52.4, 52.1, 50.0, 35.8, 26.5; anal. calcd for C₁₄H₁₆N₂O₇ (324.29): C 51.85, H 4.97, N 8.64%; found: C 51.67, H 5.05, N 8.53%.

Ethyl 3-methyl-7-morpholin-4-yl-2,4,9-trioxo-1-oxa-3-azaspiro[4.4]non-6-ene-6-carboxylate (4q). White powder (0.203 g, 60%); mp 177–180 °C (dec.); IR (KBr) (ν_{max}, cm⁻¹): 1820, 1724, 1722, 1663 (C=O), 1599 (C=C); ¹H NMR (CDCl₃, 300.1 MHz): δ_H 1.32 (3H, t, ³J_{HH} 7.1 Hz, OCH₂CH₃), 3.03 and 3.22 (2H, AB-system, ²J_{HH} 16.7 Hz, O=C-CH₂), 3.10 (3H, s, NCH₃), 3.61–3.70 (4H, m, CH₂NCH₂), 3.86 (4H, s, CH₂OCH₂), 4.25 (2H, q, ³J_{HH} 7.1 Hz, OCH₂CH₃); ¹³C NMR (CDCl₃, 75.5 MHz): δ_C 186.1, 171.1, 170.5, 163.9, 154.6, 103.7, 85.5, 66.3, 61.1, 52.2, 49.9, 35.7, 26.5, 14.2; anal. calcd for C₁₅H₁₈N₂O₇ (338.32): C 53.25, H 5.36, N 8.28%; found: C 52.97, H 5.32, N 8.25%.

Methyl 3-methyl-2,4,9-trioxo-7-thiomorpholin-4-yl-1-oxa-3-azaspiro[4.4]non-6-ene-6-carboxylate (4r). White powder (0.218 g, 64%); mp 197–199 °C (dec.); IR (KBr) (ν_{max}, cm⁻¹): 1814, 1751, 1704, 1682 (C=O), 1578 (C=C); ¹H NMR (DMSO-*d*₆, 300.1 MHz): δ_H 2.77 (4H, m, CH₂SCH₂), 2.87 (2H, m, O=CCH₂), 2.95 (3H, s, NCH₃), 3.55–3.95 (4H, m, CH₂NCH₂), 3.67 (3H, s, OCH₃); ¹³C NMR (DMSO-*d*₆, 75.5 MHz): δ_C 186.1, 171.3, 170.8, 164.5, 155.0, 102.6, 85.8, 54.1, 52.2, 51.7, 35.5, 26.9, 26.2, 26.1; anal. calcd for C₁₄H₁₆N₂O₆S (340.35): C 49.41, H 4.74, N 8.23%; found: C 49.53, H 4.69, N 8.31%.

Ethyl 3-methyl-2,4,9-trioxo-7-thiomorpholin-4-yl-1-oxa-3-azaspiro[4.4]non-6-ene-6-carboxylate (4s). White powder (0.216 g, 61%); mp 195–197 °C (dec.); IR (KBr) (ν_{max}, cm⁻¹): 1820, 1743, 1725, 1667 (C=O), 1591 (C=C); ¹H NMR (CDCl₃, 300.1 MHz): δ_H 1.31 (3H, t, ³J_{HH} 7.1 Hz, OCH₂CH₃), 2.82–2.96 (4H, m, CH₂SCH₂), 3.02 and 3.20 (2H, AB-system, ²J_{HH} 16.7 Hz, O=C-CH₂), 3.09 (3H, s, NCH₃), 3.79–3.86 (4H, m, CH₂NCH₂), 4.25 (2H, q, ³J_{HH} 7.1 Hz, OCH₂CH₃); ¹³C NMR (CDCl₃, 75.5 MHz): δ_C 186.1, 170.7, 170.5, 164.2, 154.6, 104.2, 85.4, 61.2, 55.0, 52.6, 35.8, 27.8 and 27.1, 26.5, 14.2; anal. calcd for C₁₅H₁₈N₂O₆S (354.38): C 50.84, H 5.12, N 7.91%; found: C 51.05, H 5.18, N 8.01%.

5-[(1Z)-1-Acetyl-2-(methylamino)prop-1-en-1-yl]-5-hydroxypyr-imidine-2,4,6(1H,3H,5H)-trione (6a). White powder (0.222 g, 87%); mp 149–151 °C (dec.); IR (KBr) (ν_{max}, cm⁻¹): 3439 and 3329 (NH), 3224 (OH), 1731, 1699 and 1622 (C=O), 1582 (C=C); ¹H NMR (DMSO-*d*₆, 300.1 MHz): δ_H 2.10 (3H, s, O=CCH₃), 2.49 (3H, s, =C-CH₃ overlapping with H₂O in DMSO-*d*₆), 3.01 (3H, s, NCH₃), 7.28 (1H, s, OH), 7.44 (1H, s, NH), 7.46 (1H, s, NH), 9.25 (1H, s, NH); ¹³C NMR (DMSO-*d*₆, 75.5 MHz): δ_C 191.0, 174.0, 169.8, 159.4, 152.2, 117.5, 78.6, 29.2, 26.1, 13.0; anal. calcd for C₁₀H₁₃N₃O₅ (255.22): C 47.06, H 5.13, N 16.46%; found: C 46.88, H 5.21, N 16.59%.



5-[(1Z)-1-Acetyl-2-(ethylamino)prop-1-en-1-yl]-5-hydroxypyrimidine-2,4,6(1H,3H,5H)-trione (**6b**). White powder (0.223 g, 83%); mp 168–170 °C (dec.), IR (KBr) (ν_{\max} , cm^{-1}): 3420 (NH), 3322 (OH), 1741, 1703, 1629 and 1607 (C=O), 1578 (C=C); ^1H NMR (DMSO- d_6 , 300.1 MHz): δ_{H} 1.07 (3H, t, $^3J_{\text{HH}}$ 7.0 Hz, NHCH_2CH_3), 2.10 (3H, s, $\text{O}=\text{CCH}_3$), 2.49 (3H, s, $=\text{C}-\text{CH}_3$ overlapping with H_2O in DMSO- d_6), 3.53 (2H, m, $\text{NHCH}_2-\text{CH}_3$), 7.35 (1H, s, OH), 7.46 (2H, s, 2 NH), 9.21 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , 75.5 MHz): δ_{C} 191.1, 173.9, 169.8, 158.8, 152.1, 117.7, 78.5, 34.5, 29.3, 13.9, 12.7; anal. calcd for $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_5$ (269.25): C 49.07, H 5.62, N 15.61%; found: C 48.80, H 5.65, N 15.53%.

Ethyl (2Z)-2-(5-hydroxy-2,4,6-trioxohexahydropyrimidin-5-yl)-3-(methylamino)but-2-enoate (**6c**). White powder (0.214 g, 75%); mp 175–177 °C (dec.), IR (KBr) (ν_{\max} , cm^{-1}): 3414 and 3321 (NH), 3278 (OH), 1735, 1709, 1666 and 1622 (C=O), 1586 (C=C); ^1H NMR (DMSO- d_6 , 300.1 MHz): δ_{H} 1.13 (3H, t, $^3J_{\text{HH}}$ 7.1 Hz, OCH_2CH_3), 2.49 (3H, s, $=\text{C}-\text{CH}_3$ overlapping with H_2O in DMSO- d_6), 3.00 (3H, s, NCH_3), 4.0 and 4.04 (2H, ABX₃ system, $^2J_{\text{HH}}$ 17.9 Hz, $^3J_{\text{HH}}$ 7.1 Hz, OCH_2CH_3), 7.29 (1H, s, OH) 7.44 (2H, s, 2 NH), 8.97 (1H, s, NH); ^{13}C NMR (DMSO- d_6 , 75.5 MHz): δ_{C} 174.6, 170.3, 162.6, 160.8, 152.6, 108.2, 78.5, 59.8, 26.6, 14.3, 12.7; anal. calcd for $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_6$ (285.25): C 46.32, H 5.30, N 14.73%; found: C 46.50, H 5.37, N 14.65%.

Ethyl (2Z)-3-(butylamino)-2-(5-hydroxy-2,4,6-trioxohexahydropyrimidin-5-yl)but-2-enoate (**6d**). White powder (0.223 g, 68%); mp 191–193 °C (dec.), IR (KBr) (ν_{\max} , cm^{-1}): 3369 and 3327 (NH), 3231 (OH), 1739, 1694, 1670 and 1631 (C=O); ^1H NMR (DMSO- d_6 , 300.1 MHz): δ_{H} 0.87 (3H, t, $^3J_{\text{HH}}$ 7.2 Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.13 (3H, t, $^3J_{\text{HH}}$ 7.1 Hz, OCH_2CH_3), 1.25 (2H, sex, $^3J_{\text{HH}}$ 7.1 Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.45 (2H, qu, $^3J_{\text{HH}}$ 7.1 Hz, $\text{NHCH}_2\text{CH}_2-\text{CH}_2\text{CH}_3$), 3.47 (2H, t, $^3J_{\text{HH}}$ 7.1 Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 4.0 and 4.04 (2H, ABX₃ system, $^2J_{\text{HH}}$ 17.9 Hz, $^3J_{\text{HH}}$ 7.1 Hz, OCH_2CH_3), 7.35 (1H, s, OH), 7.43 (2H, s, 2 NH), 8.93 (1H, s, NH); ^{13}C NMR (DMSO- d_6 , 75.5 MHz): δ_{C} 174.4, 169.9, 162.2, 160.0, 152.0, 108.0, 77.9, 59.3, 30.6, 19.2, 13.8, 13.5, 12.0; anal. calcd for $\text{C}_{14}\text{H}_{21}\text{N}_3\text{O}_6$ (327.33): C 51.37, H 6.47, N 12.84%; found: C 51.53, H 6.55, N 12.81%.

Conflicts of interest

There are no conflicts to declare.

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