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Double Michael addition/aza-cyclization: a valuable sequence for the construction of symmetrical and unsymmetrical spirobarbiturate-pyridines

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ABSTRACT

A simple one-pot procedure for the preparation of symmetrical bis-hydrazone functionalized barbiturates, and a step-by step sequence for the synthesis of analogous unsymmetrical derivatives were developed. Their treatment in acid conditions furnish the symmetrical- and unsymmetrical-spirobarbiturate-pyridines, respectively.

1. Introduction

Barbituric acid derivatives, commonly called barbiturates, are known to be an important class of compound that act as central nervous system depressants.[1] For this reason, they are currently used as sedatives, anesthetic, anxiolytic, and anticonvulsant agents.[1,2] In addition, these molecules are of great interest for their pharmacological activity as analeptics, immunomodulating, anti-AIDA, and anticancer agents.[3]

In particular, spirobarbiturates are biologically active molecules with important pharmacological and physiological properties.[4] It is noteworthy that spirocyclic compounds can be precursors of a variety of cyclic products by rearrangement reactions due to their steric strain associated with the quaternary carbon.[5] Therefore, many efforts were done by the researchers to synthesize spiro rings in which several five- or six-membered aza-heterocycles are fused at the 3-position of the barbituric nucleus.[4]

Among them, 1,4-dihydropyridines are of particular importance because they are used in the treatment of cardiovascular diseases such as angina, hypertension or arrhytmia[6] and they exhibit calcium-channel modulatory properties.[7] Besides, they also show antibacterial, anticancer, antileishmanial, anticoagulant, anticonvulsant, antitubercular, antioxidant, antiulcer, CFTR, antimalarials, and neuroprotection properties, as well as HIV-1 protease inhibitors, and antifertility activities.[6]

Recently, we have reported a practical two step synthesis of new and biologically interesting symmetrical 2-oxo-spiro[indole-3,4′-pyridines], starting from some oxindole derivatives with 2 equiv of 1,2-diaza-1,3-dienes, by means of a double Michael addition/cyclization sequence (Scheme 1).[8]

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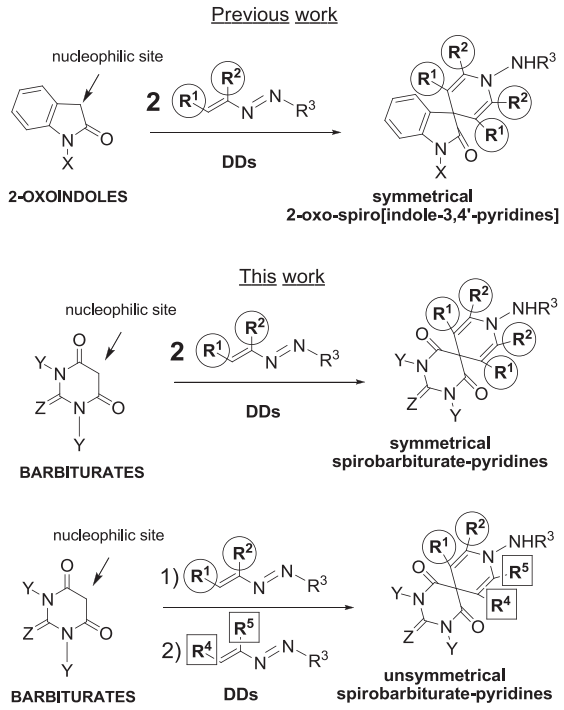


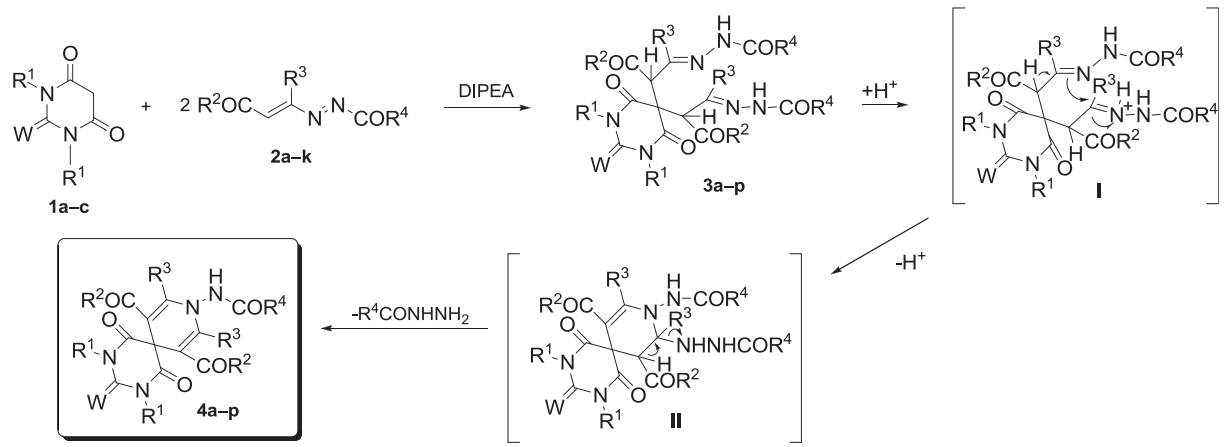
Scheme 1. Some spiro-derivatives from 1,2-diaza-1,3-dienes.

Based on our experience in the field of 1,2-diaza-1,3-dienes (DDs),[9] and to complement these investigations, we planned a synthetic strategy to obtain symmetrical spirobarbiturate-pyridines, starting from some barbiturate derivatives and 2 equiv of DDs (Scheme 1).[8] Besides, we have designed a step-by-step procedure to synthesize unsymmetrical spirobarbiturate-pyridines, by means of two sequential and distinct additions of the same nucleophilic centre of barbiturates to two different molecules of DDs, followed by the cyclization process (Scheme 1). Although in the literature many examples of spirobarbiturate-heterocycles are reported,[4] spirobarbiturate-pyridine derivatives are not well represented.[10] For this reason, the synthesis here reported can be considered of particular appeal.

2. Results and discussion

In order to obtain the target compounds, we explored the reactions between 1,3-dimethylbarbituric acid **1a**, 1,3-diethyl-2-thiobarbituric acid **1b** or 1,3-dicyclohexylbarbituric acid **1c** with DDs **2a**–**k**. The conditions we have used are the same as those tested for the synthesis of 2-oxo-spiro[indole-3,4′-pyridines][8] that foresaw the use of 1 equiv of the nucleophiles **1**, 4.4 equiv of DDs **2** and 2.2 equiv of DIPEA as promoter, in dichloromethane as solvent.

In this manner, symmetrical bis-hydrazones **3a**–**p** were prepared in good to excellent yields (54–100%) and the reactions were completed in 3.0–4.0 h (Scheme 2, Table 1). Derivatives **3a**–**p** were then treated with a catalytic amount of trifluoroacetic acid using dichloromethane as solvent to furnish the desired 1,3,5-trioxo-



Scheme 2. Synthesis of symmetrical bis-hydrazones **3a**–**p**, and of symmetrical spirobarbiturate-pyridines **4a**–**p**.

Table 1
Yields and reaction times for the synthesis of symmetrical bis-hydrazones **3a**–**p** and symmetrical spirobarbiturate-pyridines **4a**–**p**

Entry	Barbiturate **1**			DD **2**				Bis-hydrazones **3**[a]			**4**[c]		
		R^1	W		R^2	R^3	R^4		Yield (%)[b]	Time (h)		Yield (%)[d]	Time (h)
1	**1a**	Me	O	**2a**	OMe	Me	O*t*-Bu	**3a**	100	3.0	**4a**	100	16.0
2	**1a**	Me	O	**2b**	OEt	Me	O*t*-Bu	**3b**	78	3.0	**4b**	64	18.0
3	**1a**	Me	O	**2c**	OMe	Et	O*t*-Bu	**3c**	74	3.5	**4c**	62	12.0
4	**1a**	Me	O	**2d**	OMe	Me	NHPh	**3d**	65	3.0	**4d**	62	12.0
5	**1a**	Me	O	**2e**	OMe	Me	NH_2	**3e**	90	4.0	**4e**	63	12.5
6	**1a**	Me	O	**2f**	OEt	Me	NH_2	**3f**	70	3.0	**4f**	62	13.0
7	**1b**	Et	S	**2d**	OMe	Me	NHPh	**3g**	54	4.0	**4g**	96	15.0
8	**1b**	Et	S	**2g**	OEt	Me	NHPh	**3h**	57	3.0	**4h**	84	14.0
9	**1b**	Et	S	**2h**	O*i*-Pr	Me	NHPh	**3i**	62	3.0	**4i**	72	14.0
10	**1b**	Et	S	**2i**	O*t*-Bu	Me	NHPh	**3j**	92	4.0	**4j**	81	12.0
11	**1b**	Et	S	**2j**	*O*-Allyl	Me	NHPh	**3k**	92	3.5	**4k**	62	15.0
12	**1b**	Et	S	**2f**	OEt	Me	NH_2	**3l**	71	3.0	**4l**	68	17.5
13	**1c**	Cyclohexyl	O	**2d**	OMe	Me	NHPh	**3m**	82	4.0	**4m**	61	16.0
14	**1c**	Cyclohexyl	O	**2g**	OEt	Me	NHPh	**3n**	64	3.5	**4n**	73	14.0

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Table 1 (*continued*)

Entry	Barbiturate **1**			DD **2**				Bis-hydrazones **3**[a]			**4**[c]		
		R^1	W		R^2	R^3	R^4		Yield (%)[b]	Time (h)		Yield (%)[d]	Time (h)
15	**1c**	Cyclohexyl	O	**2j**	*O*-Allyl	Me	NHPh	**3o**	61	4.0	**4o**	65	12.0
16	**1c**	Cyclohexyl	O	**2k**	OMe	Et	NHPh	**3p**	73	3.0	**4p**	72	13.5

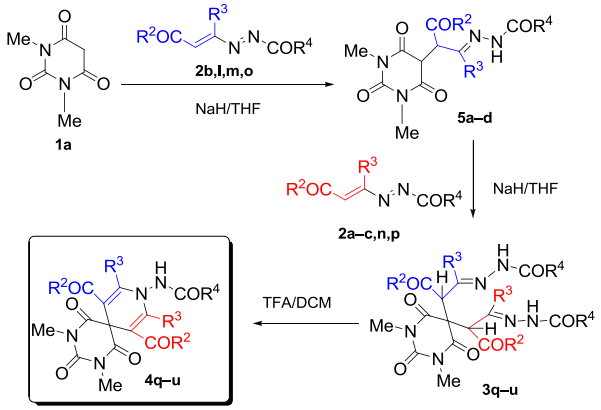
[a] Reagents and conditions: room temperature, **1a**–**c** (1.0 mmol), **2a**–**k** (4.4 mmol), DIPEA (2.2 mmol) in DCM (6 mL).
[b] Yield of pure isolated bis-hydrazones **3** referred to **1a**–**c**.
[c] Reagents and conditions: room temperature, **3a**–**p** (1.0 mmol), TFA (0.15 mmol) in DCM (6 mL).
[d] Yield of pure isolated spirobarbiturate-pyridines **4** referred to **3a**–**p**.

2,4,9-triazaspiro[5.5]undeca-7,10-dienes **4a**–**p** (here also named spirobarbiturate-pyridines), in 12.0–18.0 h in good to excellent yields (61–100%) (Scheme 2, Table 1).

Compounds **3** are formed by means of a double Michael addition of the carbon in position 3 of the barbiturate **1** to the terminal carbon atom of the azo-ene system of two molecules of the DD **2**. The loss of the proton in the α position to the hydrazone of **3** that acts as nucleophile promotes the intramolecular ring closure by means of nucleophilic attack of the sp^2 hydrazonic nitrogen to the other hydrazone moiety, activated by the acidic treatment (intermediate **I**), with the formation of the non-isolable derivative **II** (Scheme 2). The final loss of the hydrazine residue furnishes the desired spirobarbiturate-pyridines **4**.

Besides, to tentatively obtain unsymmetrical spirobarbiturate-pyridines, a step-by-step procedure involving the formation of mono-adduct hydrazonic derivatives was also projected.

With this aim, a model reaction between 1,3-dimethylbarbituric acid **1a** and DD **2b** was chosen in order to optimize the conditions for the synthesis of the mono-hydrazone **5a** (Table 2). All the reactions were carried out in tetrahydrofuran as solvent, by using a molar ratio of 1:1 referred to **1a** and **2b** upon the influence of various bases in different molar ratios. In particular, we have tested DIPEA, DBU, K_2CO_3, MeONa, *t*-BuOK, and NaH (Table 2). In all cases, the desired mono-hydrazone **5a** was achieved (Scheme 3), resulting

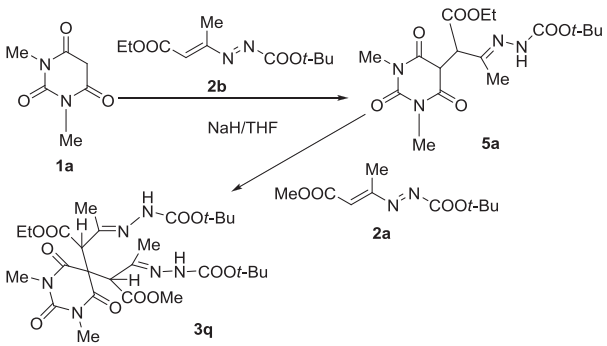


Scheme 3. Synthesis of hydrazones **5a**–**d**, unsymmetrical bis-hydrazones **3q**–**u**, and of unsymmetrical spirobarbiturate-pyridines **4q**–**u**.

from the Michael-type nucleophilic attack of the barbiturate **1a** to 1 equiv of the DD **2b**, but the best results in terms of higher yield and lower reaction time were obtained with 0.05 equiv of NaH (Table 2, entry 9). When DIPEA was employed, also the formation of the symmetrical bis-hydrazone **3b** was observed (Table 2, entries 1,2).

In an analogous manner, we also optimized the conditions to obtain unsymmetrical bis-hydrazone **3q**, by reacting compound **5a**

Table 2
Screening of different conditions for the formation of **5a**[a] and of **3q**[b]



Entry	Base	Amount of base[c]	**5a** yield (%)[d]	**5a** Time (h)	**3q** yield (%)[f]	**3q** Time (h)
1	DIPEA	1.1 equiv	38 (12)[e]	4.0	24	4.0
2	DIPEA	2.2 equiv	36 (18)[e]	3.0	31	3.0
3	DBU	1.1 equiv	21	2.5	30	2.5
4	K_2CO_3	2.0 equiv	27	6.0	19	7.5
5	K_2CO_3	4.0 equiv	31	5.5	34	7.0
6	MeONa	0.1 equiv	53	0.5	27	0.7
7	*t*-BuONa	0.1 equiv	57	0.5	32	0.7
8	NaH	0.1 equiv	87	0.1	89	0.2
9	**NaH**	**0.05 equiv**	**93**	**0.1**	**93**	**0.2**

[a] Reagents and conditions: room temperature, **1a** (1.0 mmol), **2b** (1.0 mmol) in 4 mL of THF.
[b] Reagents and conditions: room temperature, **5a** (1.0 mmol), **2a** (1.3 mmol) in 15 mL of THF.
[c] Amount referred to 1 equiv of **1a** or **5d**.
[d] Yields of isolated **5a** based on barbiturate **1a**.
[e] Yield of isolated symmetrical bis-hydrazone **3b**.
[f] Yields of isolated **3q** based on mono-hydrazone **5a**.

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with DD **2a** (Table 2). In this screening, we have found that the best conditions were the same as those employed for the synthesis of mono-adduct **5a** (0.05 equiv of NaH, in THF).

With these optimal conditions in hand, we have explored the reactions between the same 1,3-dimethylbarbituric acid **1a** and DDs **2b**,**l**,**m**,**o** (Scheme 3, Table 3). Hydrazones **5a**–**d** were obtained in excellent yields (85–97%) in 0.15–0.2 h (Scheme 3, Table 3). These latter derivatives **5a**–**d** were then reacted with a different molecule of DD **2a**–**c**,**n**,**p**, under the same conditions used for the synthesis of monoadducts **5** (THF/NaH, 0.05 equiv), achieving unsymmetrical bis-hydrazones **3q**–**u** in excellent yields (85–97%), in 2.0–4.0 h (Scheme 3, Table 3).

Table 3
Yields and reaction times for the synthesis of hydrazones **5a**–**d**, unsymmetrical bis-hydrazones **3q**–**u**, and of unsymmetrical spirobarbiturate-pyridines **4q**–**u**

Entry	1	2				5[a]			2				3[c]			4[e]		
			R^2	R^3	R^4		Yield (%)[b]	Time (h)		R^2	R^3	R^4		Yield (%)[d]	Time (h)		Yield (%)[f]	Time (h)
1	**1a**	**2b**	OEt	Me	O*t*-Bu	**5a**	88	0.15	**2a**	OMe	Me	O*t*-Bu	**3q**	93	4.0	**4q**	91	14.0
2	**1a**	**2b**	OEt	Me	O*t*-Bu	**5a**			**2c**	OMe	Et	O*t*-Bu	**3r**	91	2.0	**4r**	92	12.0
3	**1a**	**2l**	O*i*-Pr	Me	O*t*-Bu	**5b**	85	0.2	**2b**	OEt	Me	O*t*-Bu	**3s**	85	4.0	**4s**	85	16.0
4	**1a**	**2m**	OMe	Et	OMe	**5c**	97	0.2	**2n**	OEt	Me	OMe	**3t**	77	2.5	**4t**	83	14.0
5	**1a**	**2o**	OEt	Me	OEt	**5d**	87	0.15	**2p**	OMe	Me	OEt	**3u**	97	3.0	**4u**	83	13.0

[a] Reagents and conditions: room temperature, **1a** (1.0 mmol), **2b**,**l**,**m**,**o** (1.0 mmol), NaH (0.05 mmol) in 4 mL of THF.
[b] Yield of pure isolated hydrazones **5** referred to **1a**.
[c] Reagents and conditions: room temperature, **5a**–**d** (1.0 mmol), **2a**–**c**,**n**,**p** (1.3 mmol), NaH (0.05 mmol) in 15 mL of THF.
[d] Yield of pure isolated bis-hydrazones **3q**–**u** referred to **5a**–**d**.
[e] Reagents and conditions: room temperature, **3q**–**u** (1.0 mmol), TFA (0.15 mmol) in 6 mL of DCM.
[f] Yield of pure isolated unsymmetrical spirobarbiturate-pyridines **4q**–**u** referred to **3q**–**u**.

The final acidic treatment of compounds **3q**–**u** with 0.15 equiv of TFA in DCM as solvent furnished the desired unsymmetrical spirobarbiturate-pyridines **4q**–**u**, in 12.0–16.0 h in excellent yields (83–92%) (Scheme 3, Table 3).

We have also tried to conduct the reaction to prepare unsymmetrical compounds **4q**–**u** in one-pot, by not isolating **3** and treating the crude bis-hydrazones **3** directly with TFA. Unfortunately, only complicated reaction mixtures were obtained in this manner.

It is noteworthy that, in order to avoid the formation of a mixture of two different spirobarbiturate-pyridines, it is necessary that the substituent on the nitrogen in position 1 of the DDs **2** is the same in both the DDs employed in this synthesis.

3. Conclusion

In conclusion, this work represents a simple procedure for the preparation of symmetrical and unsymmetrical spirobarbiturate-pyridines by reaction between barbiturates and 1,2-diaza-1,3-dienes. These reactions proceed under mild conditions without complicated work-up procedures. The advantage of the use of 1,2-diaza-1,3-dienes as building blocks in the construction of these spiroderivatives is the stability and the easy accessibility of both the starting materials as well as of the intermediates.

It is noteworthy that these symmetrical and unsymmetrical spirobarbiturate-pyridines are not easily available from other methods, as evidenced by the poor examples reported in the literature.[10]

4. Experimental section

All the commercially available reagents and solvents were used without further purification. 1,2-Diaza-1,3-dienes **2a**–**p** were synthesized as a mixture of *E*/*Z* isomers as previously reported.[11,12] 1,3-Dimethylbarbituric acid **1a**, 1,3-diethyl-2-thiobarbituric acid **1b** and 1,3-dicyclohexylbarbituric acid **1c** are commercial materials and were used without further purification. Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulfuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100.56 MHz, respectively. Proton and carbon spectra were referenced internally to solvent signals, using values of δ=2.50 ppm for proton (middle peak) and δ=39.50 ppm for carbon (middle peak) in DMSO-d_6 and δ=7.27 ppm for proton and δ=77.00 ppm for carbon (middle peak) in $CDCl_3$. The following abbreviations are used to describe peak patterns where appropriate: s=singlet, d=doublet, *t*=triplet q=quartet, sex=sextet, hept=heptet, m=multiplet and br=broad signal. All coupling constants (*J*) are given in Hz. FTIR spectra were obtained as Nujol mulls. Mass spectra were recorded in the EI mode (70 eV). Melting points were determined in open capillary tubes.

4.1. General procedure for the synthesis of symmetrical bis-hydrazones (3a–p)

A mixture of 1,3-dimethylbarbituric acid **1a**, 1,3-diethyl-2-thiobarbituric acid **1b** or 1,3-dicyclohexylbarbituric acid **1c** (1 mmol), 1,2-diaza-1,3-diene **2a**–**k** (4.4 mmol), and DIPEA (2.2 mmol) was stirred at room temperature in CH_2Cl_2 (6 mL) for the appropriate time (3.0–4.0 h), until the disappearance of the reagent **1** (TLC monitoring). The crude mixture was then purified by column chromatography on silica gel to afford the products **3a**–**p** that were crystallized from diethyl ether.

*4.1.1. Di-tert-butyl 2,2′-[(1,3-dimethyl-2,4,6-trioxohexahydropyrimidine-5,5-diyl)bis(4-methoxy-4-oxobut-3-yl-2-ylidene)]dihydrazinecarboxylate (**3a**).* Yield: 612.2 mg (100%). White powder, mp: 134–135 °C, ^1H NMR (400 MHz, DMSO-d_6), δ=1.39 and 1.40 (2s, 18H, 2O*t*-Bu), 1.67 and 1.74 (2s, 6H, 2Me), 2.98 (s, 3H, NMe), 3.00 and 3.04 (2s, 3H, NMe), 3.58 and 3.63 (2s, 6H, 2OMe), 4.56 (s, 2H, 2CH), 9.68 and 9.69 (2s, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=16.6 (CH_3), 17.1 (CH_3), 26.3 (CH_3), 27.9 (CH_3), 28.1 (CH_3), 28.2 (CH_3), 52.1 (CH_3), 52.4 (CH_3), 55.8 (C), 56.1 (CH), 56.3 (CH), 79.3 (C), 79.4 (C), 146.9 (C), 148.1 (C), 150.1 (C), 151.0 (C), 152.4 (C), 152.5 (C), 167.8 (C), 168.1 (C), 168.9 (C), 169.0 (C), 169.4 (C); IR (Nujol): ν_{max}=3309, 3220, 1742, 1686 cm^{-1}; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{26}H_{41}N_6O_{11}$: 613.2828; found: 613.2825; MS *m*/*z* (%) 539 (6), 511 (13), 465 (36), 438 (21), 410 (31), 379 (100), 320 (78); anal. calcd for $C_{26}H_{40}N_6O_{11}$ (612.6296): C 50.97, H 6.58, N 13.72; found: C 50.95, H 6.57, N 13.74.

*4.1.2. Di-tert-butyl 2,2′-[(1,3-dimethyl-2,4,6-trioxohexahydropyrimidine-5,5-diyl)bis(4-ethoxy-4-oxobut-3-yl-2-ylidene)] (**3b**).* Yield: 499.5 mg (78%). White powder, mp: 187–188 °C, ^1H NMR (400 MHz, $CDCl_3$), δ=1.25 (t, *J*=7.2 Hz, 3H,

OCH_2Me), 1.26 (t, J=7.2 Hz, 3H, OCH_2Me), 1.43 (s, 9H, O*t*-Bu), 1.47 (s, 9H, O*t*-Bu), 1.73 (s, 3H, Me), 1.78 (s, 3H, Me), 3.21 and 3.28 (2s, 6H, 2NMe), 4.16–4.25 (m, 4H, $2OCH_2Me$), 4.81 and 4.86 (2s, 2H, 2CH), 7.42 (s, 2H, 2NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=13.9 (CH_3), 15.4 (CH_3), 15.9 (CH_3), 17.2 (CH_3), 26.9 (CH_3), 28.1 (CH_3), 28.2 (CH_3), 29.2 (CH_3), 56.4 (CH), 56.9 (CH), 60.6 (C), 61.0 (CH_2), 61.6 (CH_2), 62.3 (CH_2), 80.6 (C), 81.2 (C), 144.5 (C), 150.8 (C), 151.0 (C), 151.9 (C), 166.1 (C), 166.6 (C), 168.9 (C), 169.4 (C), 171.7 (C); IR (Nujol): ν_{max}=3490, 3345, 1735, 1720, 1690 cm^{-1}; MS *m*/*z* (%) 567 (9), 539 (21), 493 (38), 465 (13), 421 (63), 393 (100); anal. calcd for $C_{28}H_{44}N_6O_{11}$ (640.6828): C 52.49, H 6.92, N 13.12; found: C 52.47, H 6.91, N 13.11.

*4.1.3. Di-tert-butyl 2,2′-[(1,3-dimethyl-2,4,6-trioxohexahydropyrimidine-5,5-diyl)bis(1-methoxy-1-oxopent-2-yl-3-ylidene)]dihydrazinecarboxylate (**3c**).* Yield: 474.3 mg (74%). White powder, mp: 197–198 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.04 (t, J=7,6 Hz, 6H, OCH_2Me), 1.41 and 1.44 (2s, 18H, 2O*t*-Bu), 2.11 (q, J=7,6 Hz, 4H, OCH_2Me), 3.20 and 3.21 (2s, 6H, 2NMe), 3.77 (s, 6H, 2OMe), 4.91 (brs, 2H, 2CH), 7.42 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=8.9 (CH_3), 13.5 (CH_3), 23.1 (CH_2), 27.1 (CH_3), 27.7 (CH_3), 28.2 (CH_3), 28.4 (CH_3), 52.8 (CH_3), 54.2 (C), 57.1 (CH), 81.4 (C), 84.6 (C), 87.3 (C), 149.2 (C), 149.4 (C), 151.0 (C), 151.5 (C), 169.3 (C), 169.8 (C), 170.4 (C), 170.5 (C), 172.3 (C); IR (Nujol): ν_{max}=3309, 1742, 1686 cm^{-1}; MS *m*/*z* (%) 584 (3), 509 (4), 453 (100), 421 (64), 377 (23); anal. calcd for $C_{28}H_{44}N_6O_{11}$(640.6828): C 52.49, H 6.92, N 13.12; found: C 52.47, H 6.91, N 13.11.

*4.1.4. 2,2-[(1,3-Dimethyl-2,4,6-trioxohexahydropyrimidine-5,5-diyl) bis{3-[(anilinocarbonyl)hydrazono]butanoate} (**3d**).* Yield: 423.1 mg (65%). White powder, mp: 189–191 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.94 (s, 6H, 2Me), 3.26 and 3.30 (2s, 6H, 2NMe), 3.69 and 3.73 (2s, 6H 2 OMe), 4.69 and 4.73 (2s, 2H, 2CH), 6.99 (t, J=7.2 Hz, 1H$_{ar}$), 7.06 (t, J=6.8 Hz, 1H$_{ar}$), 7.21 (t, J=7.6 Hz, 2H$_{ar}$), 7.29 (t, 7.2 Hz, 2H$_{ar}$), 7.35 (d, J=8.0 Hz, 2H$_{ar}$), 7.48 (d, J=8,4 Hz, 2H$_{ar}$), 8.10 and 8.32 (2s, 2H, 2NH), 9.47 and 9.66 (2s, 2H, 2NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=17.0 (CH_3), 17.3 (CH_3), 29.2 (CH_3), 53.1 (CH_3), 53.2 (CH_3), 56.9 (CH), 57.4 (CH), 60.3 (C), 119.3 (CH), 119.9 (CH), 123.4 (CH), 123.6 (CH), 128.9 (CH), 137.7 (C), 137.9 (C), 144.0 (C), 144.2 (C), 150.9 (C), 151.0 (C), 153.8 (C), 153.9 (C), 168.1 (C), 169.0 (C), 169.4 (C), 169.5 (C), 170.2 (C); IR (Nujol): ν_{max}=3340, 3320, 3190, 1741, 1720, 1698, 1686 cm^{-1}; HRMS (ESI) *m*/*z* [M+H]$^+$ calcd for $C_{30}H_{35}N_8O_9$: 651.2522; found: 651.2521; MS *m*/*z* (%) 558 (31), 529 (22), 466 (52), 438 (71), 407 (100), 379 (56); anal. calcd for $C_{30}H_{34}N_8O_9$ (650.6395): C 55.38, H 5.27, N 17.22; found: C 55.41, H 5.29, N 17.19.

*4.1.5. Dimethyl 2,2-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidine-5,5-diyl)bis{3-[(aminocarbonyl)hydrazono]butanoate} (**3e**).* Yield: 448.8 mg (90%). White powder, mp: 183–185 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.79 and 1.81 (2s, 6H 2Me), 3.25 and 3.27 (2s, 6H, 2NMe), 3.71 and 3.72 (2s, 6H, 2OMe), 4.60 and 4.66 (2s, 2H, 2CH), 5.85 (brs, 4H, $2NH_2$), 8.86 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=16.5 (CH_3), 21.0 (CH_3), 29.0 (CH_3), 29.7 (CH_3), 53.0 (CH_3), 53.1 (CH_3), 56.6 (C), 57.0 (CH), 143.9 (C), 144.0 (C), 150.9 (C), 157.6 (C), 168.8 (C), 169.6 (C), 170.0 (C); IR (Nujol): ν_{max}=3360, 3258, 1738, 1720, 1690 cm^{-1}; MS *m*/*z* (%) 498 (M$^+$) (3), 467 (17), 438 (27), 408 (16), 379 (61), 336 (43); anal. calcd for $C_{18}H_{26}N_8O_9$ (498.4476): C 43.37, H 5.26, N 22.48; found: C 43.35, H 5.24, N 22.51.

*4.1.6. Diethyl 2,2′-[(1,3-dimethyl-4,6-dioxo-2-thioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]butanoate} (**3f**).* Yield: 368.6 mg (70%). White powder, mp: 181–183 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.21–1.27 (m, 6H, $2OCH_2Me$), 1.80 and 1.82 (2s, 6H, 2Me), 3.25 and 3.27 (2s, 6H, 2NMe), 4.09–4.19 (m, 4H, $2OCH_2Me$), 4.58 (s, 1H, CH), 4.63 (s, 1H, CH), 5.82 (brs, 4H, $2NH_2$), 8.83 and 8.88 (2s, 2H, 2NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=13.9 (CH_3), 14.2 (CH_3), 16.5 (CH_3), 16.8 (CH_3), 28.9 (CH_3), 56.7 (CH), 57.0 (CH), 57.3 (C), 60.4 (CH_2), 62.3 (CH_2), 144.1 (C), 151.0 (C), 151.3 (C), 157.7 (C), 168.1 (C), 169.0 (C), 169.4 (C), 169.5 (C); IR (Nujol): ν_{max}=3489, 3344, 3260, 1752, 1735, 1689 cm^{-1}; HRMS (ESI) *m*/*z* [M+H]$^+$ calcd for $C_{20}H_{31}N_8O_9$: 527.2209; found: 527.2207; MS *m*/*z* (%): 526 (M$^+$) (10), 435 (6), 387 (6), 300 (5), 256 (11), 213 (20), 199 (14), 185 (18), 167 (32), 149 (100); anal. calcd for $C_{20}H_{30}N_8O_9$ (526.5007): C 45.62, H 5.74, N 21.28; found: C 45.60, H 5.72, N 21.26.

*4.1.7. Dimethyl 2,2-[(1,3-dimethyl-4,6-dioxo-2-thioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]butanoate} (**3g**).* Yield: 375.0 mg (54%). White powder, mp: 189–191 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.10 (t, J=7.2 Hz, 6H, $2NCH_2Me$), 1.80 (s, 6H, 2Me), 3.65 (s, 6H, 2OMe), 4.28 (q, J=7.2 Hz, 4H, $2NCH_2Me$), 4.70 (s, 2H, 2CH), 6.97 (t, J=7.2 Hz, 2H$_{ar}$), 7.25 (t, J=7.2 Hz, 4H$_{ar}$), 7.41 (d, J=7.6 Hz, 4H$_{ar}$), 8.64 (s, 2H, 2NH), 9.79 (s, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=11.4 (CH_3), 16,6 (CH_3), 43.5 (CH_2), 52.8 (CH_3), 56.5 (CH), 57.2 (CH), 59.7 (C), 118.7 (CH), 122.3 (CH), 128.7 (CH), 128.8 (CH), 138.9 (C), 139.2 (C), 143.1 (C), 152.3 (C), 166.7 (C), 169.8 (C), 178.9 (C); IR (Nujol): ν_{max}=3358, 3310, 3195, 1740, 1689 cm^{-1}; HRMS (ESI) *m*/*z* [M+H]$^+$ calcd for $C_{32}H_{39}N_8O_8S$: 695.2606; found: 695.2604; MS *m*/*z* (%): 602 (8), 574 (6), 509 (37), 481 (29), 422 (56), 369 (100); anal. calcd for $C_{32}H_{38}N_8O_8S$ (694.7592): C 55.32, H 5.51, N 16.13; found: C 55.29, H 5.50, N 16.11.

*4.1.8. Diethyl 2,2′-[(1,3-dimethyl-4,6-dioxo-2-thioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]butanoate} (**3h**).* Yield: 412.3 mg (57%). White powder, mp: 181–183 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.20–1.26 (m, 12H, $2OCH_2Me$ and $2NCH_2Me$) 1.96 (s, 6H, 2Me), 4.15 (q, J=7.2 Hz, 4H, $2OCH_2Me$), 4.40–4.44 (m, 2H, NCH_2Me), 4.50–4.54 (m, 2H, NCH_2Me), 4.73 (s, 2H, 2CH), 7.00 (t, J=7.2 Hz, 2H$_{ar}$), 7.24 (t, J=7.6 Hz, 4H$_{ar}$), 7.37 (d, J=8.0 Hz, 4H$_{ar}$), 8.43 (s, 2H, 2NH), 9.49 (s, 2H, 2NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=11.7 (CH_3), 14.0 (CH_3), 14.1 (CH_3), 16.6 (CH_3), 29.7 (CH_3), 44.1 (CH_2), 56.8 (CH), 58.3 (CH), 61.4 (C), 62.6 (CH_2), 119.4 (CH), 123.6 (CH), 128.9 (CH), 137.6 (C), 144.1 (C), 153.3 (C), 167.2 (C), 169.5 (C), 178.8 (C); IR (Nujol): ν_{max}=3345, 3313, 3193, 1736, 1721, 1700, 1686 cm^{-1}; HRMS (ESI) *m*/*z* [M+H]$^+$ calcd for $C_{34}H_{43}N_8O_8S$: 723.2919; found: 723.2916; MS *m*/*z* (%): 629 (4), 602 (11), 537 (37), 510 (26), 436 (55), 363 (73); anal. calcd for $C_{34}H_{42}N_8O_8S$ (722.8124): C 56.50, H 5.86, N 15.50; found: C 56.48, H 5.84, N 15.47.

*4.1.9. Diisopropyl 2,2′-[(1,3-diethyl-4,6-dioxo-2-thioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]butanoate} (**3i**).* Yield: 465.2 mg (62%). White powder, mp: 185–186 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.19 (d, J=6.4 Hz, 12H, $2OCHMe_2$), 1.24 (t, J=6.8 Hz, 6H, $2NCH_2Me$), 1.95 (s, 6H, 2Me), 4.39–4.44 (m, 2H, NCH_2Me), 4.52–4.55 (m, 2H, NCH_2Me), 4.69 (s, 2H, 2CH), 4.97 (hept, J=6.4 Hz, 2H, $2OCHMe_2$), 7.00 (t, J=7.6.0 Hz, 2H$_{ar}$), 7.22 (t, J=8.4 Hz, 4H$_{ar}$), 7.37 (d, J=7.6 Hz, 4H$_{ar}$), 8.44 (s, 2H, 2NH), 9.29 (s, 2H, 2NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=11.6 (CH_3), 16.7 (CH_3), 21.4 (CH_3), 21.6 (CH_3), 26.9 (CH_3), 44.0 (CH_2), 56.7 (C), 58.6 (CH), 70.7 (CH), 119.3 (CH), 123.4 (CH), 128.9 (CH), 137.8 (C), 144.5 (C), 153.6 (C), 167.4 (C), 169.1 (C), 179.0 (C); IR (Nujol): ν_{max}=3364, 3322, 3198, 3082, 1744, 1702, 1688 cm^{-1}; MS *m*/*z* (%): 657 (6), 565 (16), 536 (6), 451 (61), 363 (100); anal. calcd for $C_{36}H_{46}N_8O_8S$ (750.8656): C 57.58, H 6.17, N 14.92; found: C 57.60, H 6.16, N 14.90.

*4.1.10. Di-tert-butyl 2,2′-[(1,3-diethyl-4,6-dioxo-2-thioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]butanoate} (**3j**).* Yield: 716.8 mg (92%). White powder, mp: 189–191 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.24 (t, J=6.8 Hz, 6H, $2NCH_2Me$), 1.37 (s, 18H, $2OMe_3$), 1.95 (s, 6H, 2Me), 4.35–4.41 (m, 2H, NCH_2Me), 4.55–4.59 (m, 2H, NCH_2Me), 4.61 (s, 2H, 2CH), 6.99 (t,

J=7.6 Hz, 2H$_{ar}$), 7.20 (t, J=7.2 Hz, 4H$_{ar}$), 7.34 (d, J=8.8 Hz, 4H$_{ar}$), 8.48 (s, 2H, 2NH), 9.27 (s, 2H, 2NH); ^{13}C NMR (100 MHz, CDCl$_3$); δ=11.5 (CH$_3$), 16.5 (CH$_3$), 26.9 (CH$_3$), 27.7 (CH$_3$), 44.0 (CH$_2$), 56.3 (C), 59.5 (CH), 83.8 (C), 119.2 (CH), 123.3 (CH), 128.8 (CH), 137.8 (C), 145.0 (C), 153.6 (C), 167.6 (C), 168.9 (C), 179.3 (C); IR (Nujol): ν_{max}=3360, 3311, 3198, 1741, 1691 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{38}H_{51}N_8O_8S$: 779.3545; found: 779.3547; MS m/z (%): 594 (16), 565 (11), 521 (41), 448 (69), 420 (38); anal. calcd for $C_{38}H_{50}N_8O_8S$ (778.9187): C 58.59, H 6.47, N 14.39; found: C 58.61, H 6.48, N 14.41.

4.1.11. Diallyl 2,2′-[(1,3-diethyl-4,6-dioxo-2-thioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]butanoate} (***3k***). Yield: 687.3 mg (92%). White powder, mp: 173–175 °C, ^{1}H NMR (400 MHz, CDCl$_3$), δ=1.13–1.25 (m, 6H, 2NCH$_2$*Me*), 1.92 and 1.94 (2s, 6H, 2Me), 4.38 (d, J=6.8 Hz, 4H, 2NC*H*$_2$Me), 4.61–4.63 (m, 4H, OAllyl), 4.68 and 4.73 (2s, 2H, 2CH), 5.20–5.31 (m, 4H, OAllyl), 5.81–5.88 (m, 2H, OAllyl), 7.06 (t, J=7.2 Hz, 2H$_{ar}$), 7.26 (t, J=8.8 Hz, 4H$_{ar}$), 7.45 (d, J=7.6 Hz, 4H$_{ar}$), 8.08 (s, 2H, 2NH), 9.13 (s, 2H, 2NH); ^{13}C NMR (100 MHz, CDCl$_3$), δ=11.5 (CH$_3$), 11.7 (CH$_3$), 16.9 (CH$_3$), 17.3 (CH$_3$), 26.9 (CH$_3$), 44.1 (CH$_2$), 57.4 (CH), 57.9 (CH), 66.9 (CH$_2$), 119.7 (CH), 120.0 (CH), 120.2 (CH), 123.7 (CH), 128.9 (CH), 130.9 (C), 137.7 (CH), 143.7 (C), 153.7 (C), 166.1 (C), 167.1 (C), 167.2 (C), 168.5 (C), 178.2 (C); IR (Nujol): ν_{max}=3361, 3310, 3195, 1739, 1690 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{36}H_{43}N_8O_8S$: 747.2919; found: 747.2916; MS m/z (%): 561 (11), 534 (6), 477 (15), 392 (63); anal. calcd for $C_{36}H_{42}N_8O_8S$ (746.8338): C 57.90, H 5.67, N 15.00; found: C 57.91, H 5.68, N 15.03.

4.1.12. Diethyl 2,2′-[(1,3-diethyl-4,6-dioxo-2-thioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]butanoate} (***3l***). Yield: 404.9 mg (71%). White powder, mp: 173–174 °C, ^{1}H NMR (400 MHz, DMSO-d_6), δ=1.04–1.20 (m, 12H, 2NCH$_2$*Me* and 2 OCH$_2$*Me*), 1.68 (s, 3H, Me), 1.76 (s, 3H, Me), 4.08–4.12 (m, 4H, 2NC*H*$_2$Me), 4.23–4.26 (m, 4H, 2OCH$_2$*Me*), 4.94 (s, 1H, CH), 4.51 (s, 1H, CH), 6.18 (brs, 4H, 2NH$_2$), 9.36 (brs, 1H, NH), 9.38 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=11.1 (CH$_3$), 11.4 (CH$_3$), 13.7 (CH$_3$), 13.9 (CH), 16.5 (CH$_3$), 17.1 (CH$_3$), 43.1 (CH$_2$), 43.4 (CH$_2$), 56.2 (CH), 56.4 (CH), 57.1 (CH$_2$), 57.7 (CH$_2$), 61.6 (C), 141.5 (C), 142.5 (C), 156.1 (C), 156.3 (C), 165.7 (C), 166.8 (C), 167.1 (C), 168.7 (C), 169.3 (C), 178.7 (C), 178.9 (C); IR (Nujol): ν_{max}=3360, 3315, 3189, 1740, 1685 cm^{-1}; MS m/z (%): 525 (26), 452 (37), 408 (49), 363 (79); anal. calcd for $C_{22}H_{34}N_8O_8S$ (570.6205): C 46.31, H 6.01, N 19.64; found: C 46.28, H 6.03, N 19.62.

4.1.13. Dimethyl 2,2′-[(1,3-dicyclohexyl-2,4,6-trioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]butanoate} (***3m***). Yield: 645.0 mg (82%). White powder, mp: 183–185 °C, ^{1}H NMR (400 MHz, CDCl$_3$), δ=1.16–1.19 (m, 2H, Cyclohexyl), 1.25–1.32 (m, 4H, Cyclohexyl), 1.61–1.70 (m, 6H, Cyclohexyl), 1.17–1.82 (m, 4H, Cyclohexyl), 1.91 (s, 6H, 2Me), 2.18–2.24 (m, 4H, Cyclohexyl), 3.67 (s, 6H, 2OMe), 4.56–4.60 (m, 2H, Cyclohexyl), 4.67 (s, 2H, 2CH), 6.85 (t, J=7.2 Hz, 2H$_{ar}$), 7.22 (t, J=7.6 Hz, 4H$_{ar}$), 7.34 (d, J=7.6 Hz, 4H$_{ar}$), 8.41 (s, 2H, 2NH), 9.20 (s, 2H, 2NH); ^{13}C NMR (100 MHz, CDCl$_3$), δ=16.8 (CH$_3$), 25.3 (CH$_2$), 26.4 (CH$_2$), 26.9 (CH$_2$), 53.0 (CH$_3$), 56.4 (CH), 56.7 (C), 57.8 (CH), 119.2 (CH), 123.4 (CH), 128.9 (CH), 137.7 (C), 144.5 (C), 150.9 (C), 153.4 (C), 169.3 (C), 170.2 (C); IR (Nujol): ν_{max}=3358, 3221, 3091, 1760, 1711, 1689 cm^{-1}; MS m/z (%): 574 (38), 477 (46), 417 (36), 403 (17); anal. calcd for $C_{40}H_{50}N_8O_9$ (786.8735): C 61.06, H 6.40, N 14.24; found: 61.08, H 6.39, N 14.26.

4.1.14. Diethyl 2,2′-(1,3-dicyclohexyl-2,4,6-trioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]butanoate} (***3n***). Yield: 521.7 mg (64%). White powder, mp: 197–198 °C, ^{1}H NMR (400 MHz, CDCl$_3$), δ=1.21 (t, J=7.2 Hz, 6H, 2OCH$_2$*Me*), 1.21–1.41 (m, 6H, Cyclohexyl), 1.61–1.70 (m, 6H, Cyclohexyl), 1.78–1.82 (m, 4H, Cyclohexyl), 1.96 (s, 6H, 2Me), 2.20–2.27 (m, 4H, Cyclohexyl), 4.10–4.16 (q, J=7.2 Hz, 4H, 2OC*H*$_2$Me), 4.58–4.64 (m, 2H, Cyclohexyl), 4.69 (s, 2H, 2CH), 6.98 (t, J=7.6 Hz, 2H$_{ar}$), 7.20 (t, J=7.6 Hz, 4H$_{ar}$), 7.34 (d, J=7.6 Hz, 4H$_{ar}$), 8.48 (s, 2H, 2NH), 9.72 (s, 2H, 2NH); ^{13}C NMR (100 MHz, CDCl$_3$), δ=13.9 (CH$_3$), 16.9 (CH$_3$), 25.3 (CH$_2$), 26.3 (CH$_2$), 26.8 (CH$_2$), 28.6 (CH$_2$), 56.3 (CH), 56.5 (C), 58.0 (CH), 62.3 (CH$_2$), 119.1 (CH), 123.2 (CH), 128.8 (CH), 137.8 (C), 145.0 (C), 151.1 (C), 153.8 (C), 169.3 (C), 169.9 (C); IR (Nujol): ν_{max}=3355, 3320, 1742, 1685 cm^{-1}; MS m/z (%): 631 (3), 603 (7), 558 (33), 529 (41), 485 (31), 456 (53); anal. calcd for $C_{42}H_{54}N_8O_9$ (814.9267): C 61.90, H 6.68, N 13.75; found: C 61.88, H 6.70, N 13.78.

4.1.15. Diallyl 2,2′-[(1,3-dicyclohexyl-2,4,6-trioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]butanoate} (***3o***). Yield: 511.5 mg (61%). White powder, mp: 191–193 °C, ^{1}H NMR (400 MHz, CDCl$_3$), δ=1.10–1.28 (m, 6H, Cyclohexyl), 1.42–1.72 (m, 10H, Cyclohexyl), 1.89 (s, 6H, 2Me), 2.13–2.19 (m, 6H, Cyclohexyl), 4.59–4.65 (m, 6H, Cyclohexyl and 2 CH), 5.23 (d, J=10.4 Hz, 2H, OAllyl), 5.29 (d, J=16.8 Hz, 2H, OAllyl), 5.82–5.90 (m, 2H, OAllyl), 7.07 (t, J=7.6 Hz, 2H$_{ar}$), 7.31 (t, J=7.2 Hz, 4H$_{ar}$), 7.49 (d, J=7.6 Hz, 4H$_{ar}$), 8.09 (brs, 2H, 2NH), 8.50 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, CDCl$_3$), δ=17.3 (CH$_3$), 25.4 (CH$_2$), 26.4 (CH$_2$), 26.5 (CH$_2$), 26.7 (CH$_2$), 27.1 (CH$_2$), 28.8 (CH$_2$), 29.0 (CH$_2$), 56.7 (CH), 56.9 (C), 57.5 (C), 57.9 (CH), 67.0 (CH$_2$), 119.8 (CH), 120.2 (CH), 120.3 (CH$_2$), 124.0 (CH), 128.9 (CH), 129.1 (CH), 131.2 (C), 132.1 (C), 137.9 (C), 144.0 (C), 151.3 (C), 153.6 (C), 168.1 (C), 169.0 (C), 169.6 (C); IR (Nujol): ν_{max}=3350, 3220, 3092, 1746, 1700, 1689 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{44}H_{55}N_8O_9$: 839.4087; found: 839.4088; MS m/z (%): 627 (5), 541 (16), 485 (26), 457 (16); anal. calcd for $C_{44}H_{54}N_8O_9$ (838.9481): C 62.99, H 6.49, N 13.36; found: C 63.01, H 6.48, N 13.39.

4.1.16. Dimethyl 2,2′-[(1,3-dicyclohexyl-2,4,6-trioxohexahydropyrimidine-5,5-diyl)bis{3-[(anilinocarbonyl)hydrazono]pentanoate} (***3p***). Yield: 594.1 mg (73%). White powder, mp: 191–192 °C, ^{1}H NMR (400 MHz, CDCl$_3$), δ=1.04 (t, J=7.2 Hz, 6H, 2OCH$_2$*Me*), 1.13–1.18 (m, 2H, Cyclohexyl), 1.25–1.33 (m, 2H, Cyclohexyl), 1.61–1.68 (m, 6H, Cyclohexyl), 1.71–1.80 (m, 6H, Cyclohexyl), 2.02–2.20 (m, 6H, Cyclohexyl and OC*H*$_2$Me), 2.40–2.50 (m, 2H, OC*H*$_2$Me), 3.66 and 3.75 (2s, 6H, 2OMe), 4.51–4.60 (m, 2H, Cyclohexyl), 4.67 and 4.70 (2s, 2H, 2CH), 7.02 and 7.11 (2t, J=7.6 Hz, 2H$_{ar}$), 7.26 and 7.34 (2t, J=7.6 Hz, 4H$_{ar}$), 7.41 and 7.49 (2d, J=7.6 Hz, 4H$_{ar}$), 8.06 and 8.50 (2 brs, 2H, 2NH), 8.58 and 8.82 (2 brs, 2H, 2NH); ^{13}C NMR (100 MHz, CDCl$_3$), δ=8.94 (CH$_3$), 9.40 (CH$_3$), 23.6 (CH$_2$), 23.8 (CH$_2$), 25.3 (CH$_2$), 26.1 (CH$_2$), 26.3 (CH$_2$), 28.6 (CH$_2$), 28.7 (CH$_2$), 52.8 (CH$_3$), 53.0 (CH$_3$), 56.5 (C), 56.8 (CH), 57.2 (CH), 57.3 (CH), 119.3 (CH), 120.3 (CH), 123.4 (CH), 123.8 (CH), 128.9 (CH), 137.7 (C), 137.9 (C), 148.7 (C), 150.8 (C), 151.1 (C), 153.3 (C), 153.4 (C), 167.7 (C), 169.1 (C), 169.7 (C), 170.2 (C); IR (Nujol): ν_{max}=3360, 3218, 3093, 1751, 1703, 1690 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{42}H_{55}N_8O_9$: 815.4087; found: 815.4086; MS m/z (%): 694 (3), 602 (14), 573 (31), 514 (81), 456 (100); anal. calcd for $C_{42}H_{54}N_8O_9$ (814.9267): C 61.90, H 6.68, N 13.75; found: C 61.93, H 6.70, N 13.77.

4.2. General procedure for the synthesis of mono-hydrazones (5a–d)

A mixture of 1,3-dimethylbarbituric acid **1a** (1.0 mmol) and 1,2-diaza-1,3-diene **2b**,**l**,**m**,**o** (1.0 mmol) was stirred at room temperature in THF (4.0 mL) and a catalytic amount of sodium hydride (0.05 equiv) was added. The reaction was completed in 2–5 min (TLC monitoring) as also evidenced by the disappearance of the typical red color of the azo-ene system. To the crude mixture was then added diethl ether (4.0 mL) and cyclohexane (4.0 mL) and the solution was stirred for an additional time of 4.0–6.0 h until a white

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solid precipitate was formed. The filtration under vacuo of the crude provided the pure hydrazone derivatives **5a**–**d**.

*4.2.1. tert-Butyl 2-[2-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-3-ethoxy-1-methyl-3-oxopropylidene]hydrazinecarboxylate (**5a**).* Yield: 351.0 mg (88%). White powder, mp: 161–163 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.34 (t, J=7,2 Hz, 3H, OCH_2Me), 1.41 (s, 9H, $OCMe_3$), 1.93 (s, 3H, Me), 3.29 (s, 6H, 2NMe), 4.09 (d, J=3.6 Hz, 1H, CH), 4.27–4.33 (m, 2H, OCH_2Me), 4.36 (d, J=3.2 Hz, 1H, CH), 7.38 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=14.0 (CH_3), 15.7 (CH_3), 28.1 (CH_3), 28.4 (CH_3), 28.6 (CH_3), 49.0 (CH), 53.0 (CH), 61.8 (CH_2), 80.9 (C), 143.4 (C), 151.2 (C), 151.6 (C), 167.4 (C), 167.6 (C), 170.0 (C); IR (Nujol): ν_{max}=3360, 3220, 3092, 1758, 1710, 1691 cm^{-1}; MS m/z (%): 398 (M^+) (4), 325 (16), 296 (13), 279 (56), 252 (77), 223 (100); anal. calcd for $C_{17}H_{26}N_4O_7$ (398.4111): C 51.25, H 6.58, N 14.06; found: C 51.27, H 6.60, N 14.09.5.

*4.2.2. Ethyl 2-[2-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-1-ethyl-3-methoxy-3-oxopropylidene]hydrazinecarboxylate (**5b**).* Yield: 303.1 mg (85%). White powder, mp: 188–189 °C, ^{1}H NMR (400 MHz, DMSO-d_6), δ=0.87 (t, J=7.2 Hz, 3H, OCH_2Me), 2.15–2.19 and 2.48–2.63 (2m, 2H, OCH_2Me), 3.09 and 3.10 (2s, 6H, 2NMe), 3.56 (s, 3H, OMe), 3.67 (s, 3H, OMe), 4.32 (d, J=3.6 Hz, 1H, CH), 4.36 (d, J=3.6 Hz, 1H, CH), 10.11 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=8.6 (CH_3), 22.1 (CH_2), 27.8 (CH_3), 28.1 (CH_3), 48.6 (CH), 49.7 (CH), 52.0 (CH_3), 150.1 (C), 151.5 (C), 154.4 (C), 167.4 (C), 170.3 (C); IR (Nujol): ν_{max}=3360, 3222, 3102, 1760, 1715, 1689 cm^{-1}; MS m/z (%): 356 (M^+) (5), 324 (12), 311 (36), 279 (54), 251 (61); anal. calcd for $C_{14}H_{20}N_4O_7$ (356.3314): C 47.19, H 5.66, N 15.72; found: C 47.17, H 5.67, N 15.74.

*4.2.3. 1,1-Dimethylpropyl 2-[2-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-3-isopropoxy-1-methyl-3-oxopropylidene]hydrazinecarboxylate (**5c**).* Yield: 399.8 mg (97%). White powder, mp: 177–178 °C, ^{1}H NMR (400 MHz, DMSO-d_6), δ=1.18 (d, J=6.0 Hz, 3H, $OCHMe_2$), 1.21 (d, J=6.4 Hz, 3H, $OCHMe_2$), 1.37 (s, 9H, $OCMe_3$), 1.84 (s, 3H, Me), 3.06 (s, 6H, 2NMe), 4.22 (d, J=2.8 Hz, 1H, CH), 4.27 (d, J=2.8 Hz, 1H, CH), 4.96 (hept, J=6.4 Hz, 1H, $OCHMe_2$), 9.64 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=17.6 (CH_3), 22.0 (CH_3), 22.1 (CH_3), 28.5 (CH_3), 28.6 (CH_3), 28.8 (CH_3), 49.4 (CH), 53.4 (CH), 68.9 (CH), 79.9 (C), 146.4 (C), 152.1 (C), 153.3 (C), 168.0 (C), 168.4 (C), 169.8 (C); IR (Nujol): ν_{max}=3342, 3221, 1760, 1718, 1688 cm^{-1}; MS m/z (%): 412 (M^+) (2), 339 (14), 311 (18), 294 (61), 251 (100); anal. calcd for $C_{18}H_{28}N_4O_7$ (412.4377): C 52.42, H 6.84, N 13.58; found: C 52.43, H 6.82, N 13.56.

*4.2.4. Ethyl 2-[2-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-3-ethoxy-1-methyl-3-oxopropylidene]hydrazinecarboxylate (**5d**).* Yield: 322.1 mg (87%). White powder, mp: 177–178 °C, ^{1}H NMR (400 MHz, DMSO-d_6), δ=1.13 (t, J=7.2 Hz, 3H, OCH_2Me), 1.20 (t, J=7.2 Hz, 3H, OCH_2Me), 1.76 (s, 3H, Me), 3.08 (s, 6H, 2NMe), 3.99–4.07 (m, 3H, OCH_2Me and CH), 4.09–4.16 (m, 3H, OCH_2Me and CH), 9.92 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=13.9 (CH_3), 14.5 (CH_3), 16.9 (CH_3), 28.1 (CH_3), 28.2 (CH_3), 49.6 (CH), 52.3 (CH), 60.5 (CH_2), 60.7 (CH_2), 146.1 (C), 151.5 (C), 153.8 (C), 167.4 (C), 167.6 (C), 169.6 (C); IR (Nujol): ν_{max}=3358, 3220, 3100, 1758, 1720, 1685 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{23}N_4O_7$: 371.1561; found: 371.1561; MS m/z (%): 370 (M^+) (4), 325 (31), 296 (43), 280 (78), 251 (100); anal. calcd for $C_{15}H_{22}N_4O_7$ (370.3579): C 48.64, H 5.99, N 15.13; found: C 48.65, H 6.01, N 15.11.

4.3. General procedure for the synthesis of unsymmetrical bis-hydrazones (3q–u)

Hydrazonic compounds **5a**–**d** (1.0 mmol) were dissolved in THF (15 mL) with a different 1,2-diaza-1,3-diene **2a**–**c**,**n**,**p** (1.3 mmol) and a catalytic amount of sodium hydride (0.05 equiv) was added. The mixture was allowed to stand in these conditions for 4.0–6.0 h, until the disappearance of the **5** (TLC monitoring). The crude mixture was purified by column chromatography on silica gel to afford the unsymmetrical bis-hydrazones **3q**–**u** that were crystallized from diethyl ether-light petroleum (bp 40–60 °C).

*4.3.1. 1,1-Dimethylpropyl 2-(2-{5-[2-[(tert-butoxycarbonyl)hydrazono]-1-(ethoxycarbonyl)propyl]-1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl}-3-methoxy-1-methyl-3-oxopropylidene)hydrazinecarboxylate (**3q**).* Yield: 581.1 mg (93%). White powder, mp: 168–170 °C, ^{1}H NMR (400 MHz, DMSO-d_6), δ=1.13 (q, J=7.2 Hz, 3H, OCH_2Me), 1.39, 1.40 and 1.41 (3s, 18H, $2OCMe_3$), 1.68 and 1.73 (2s, 6H, 2Me), 2.95, 3.01 and 3.04 (3s, 6H, 2NMe), 3.60 and 3.62 (2s, 3H, OMe), 4.02–4.13 (m, 2H, OCH_2Me), 4.52 (brs, 1H, CH), 4.60 (brs, 1H, CH), 9.68 (brs, 1H, NH), 9.69 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=13.7 (CH_3), 16.9 (CH_3), 17.2 (CH_3), 27.9 (CH_3), 28.1 (CH_3), 28.2 (CH_3), 28.3 (CH_3), 28.4 (CH_3), 52.4 (C), 56.1 (CH_3), 56.3 (CH_3), 60.8 (CH_2), 61.2 (CH_2), 79.3 (C), 79.4 (C), 150.1 (C), 151.0 (C), 152.4 (C), 152.5 (C), 168.0 (C), 168.9 (C), 169.0 (C), 169.4 (C); IR (Nujol): ν_{max}=3660, 3218, 1758, 1705, 1690 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{43}N_6O_{11}$: 627.2984; found: 627.2984; MS m/z (%): 567 (22), 494 (35), 465 (31), 463 (18), 418 (86), 390 (72); anal. calcd for $C_{27}H_{42}N_6O_{11}$ (626.6562): C 51.75, H 6.76, N 13.41; found: C 51.77, H 6.75, N 13.43.

*4.3.2. tert-Butyl 2-(2-{5-[2-[(tert-butoxycarbonyl)hydrazono]-1-(ethoxycarbonyl)propyl]-1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl}-1-ethoxy-3-methoxy-3-oxopropylidene)hydrazinecarboxylate (**3r**).* Yield: 581.9 mg (91%). White powder, mp: 191–193 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=0.78–0.83 (m, 3H, CH_2Me), 1.08–1.19 (m, 3H, OCH_2Me), 1.38, 1.40 and 1.41 (3s, 18H, $2OCMe_3$), 1.64 and 1.70 (2s, 3H, Me), 2.40–2.46 (m, 2H, OCH_2Me), 2.97, 2.98, 2.99 and 3.00 (4s, 6H, 2NMe), 3.61 and 3.62 (2s, 3H, OMe), 3.99–4.12 (m, 2H, OCH_2Me), 4.55 (brs, 1H, CH), 4.77 (brs, 1H, CH), 9.70, 9.78 and 9.81 (3 brs, 2H, 2NH); IR (Nujol): ν_{max}=3358, 3221, 1763, 1712, 1688 cm^{-1}; MS m/z (%): 567 (M^+) (6), 538 (4), 465 (35), 437 (44), 393 (59); anal. calcd for $C_{28}H_{44}N_6O_{11}$ (640.6828): C 52.49, H 6.92, N 13.12; found: C 52.51, H 6.93, N 13.14.

*4.3.3. tert-Butyl 2-(2-{5-[2-[(tert-butoxycarbonyl)hydrazono]-1-(ethoxycarbonyl)propyl]-1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl}-3-isopropoxy-1-methyl-3-oxopropylidene)hydrazinecarboxylate (**3s**).* Yield: 555.2 mg (85%). White powder, mp: 191–193 °C, ^{1}H NMR (400 MHz, DMSO-d_6), δ=1.05–1.12 (m, 9H, $OCHMe_2$ and OCH_2Me), 1.42 (s, 18H, $2OCMe_3$), 1.83 (s, 6H, 2Me), 3.02 (s, 6H, 2NMe), 3.87–3.92 and 4.00–4.04 (2m, 2H, $2OCH_2Me$), 4.27 (s, 1H, CH), 4.31 (s, 1H, CH), 4.83 (hept, J=6.4 Hz, 1H, $OCHMe_2$), 9.53 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=13.7 (CH_3), 17.1 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 28.0 (CH_3), 28.1 (CH_3), 28.2 (CH_3), 28.3 (CH_3), 56.1 (CH), 56.5 (CH), 56.7 (C), 60.8 (CH_2), 61.1 (CH), 79.3 (C), 79.4 (C), 151.1 (C), 152.5 (C), 152.6 (C), 168.1 (C), 168.3 (C), 168.9 (C), 169.0 (C); IR (Nujol): ν_{max}=3360, 3220, 1765, 1718, 1691 cm^{-1}; MS m/z (%): 581 (19), 509 (11), 480 (41), 421 (65), 393 (71); anal. calcd for $C_{29}H_{46}N_6O_{11}$ (654.7094): C 53.20, H 7.08, N 12.84; found: C 53.17, H 7.09, N 12.86.

*4.3.4. Methyl 2-[2-(5-{1-(ethoxycarbonyl)-2-[(methoxycarbonyl)hydrazono]propyl}-1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-1-ethyl-3-methoxy-3-oxopropylidene]hydrazinecarboxylate (**3t**).* Yield: 427.2 mg (77%). White powder, mp: 188–190 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=0.95 (t, J=7.6 Hz, 3H, CH_2Me), 1.15–1.27 (m, 5H, OCH_2Me and CH_2Me), 1.76 and 1.78 (2s, 6H, 2NMe), 2.01 (s, 3H, Me), 3.17 and 3.23 (2s, 6H, 2OMe), 3.72 and 3.74 (2s, 3H, OMe), 4.07–4.10 (m, 2H, OCH_2Me), 4.62 (brs, 1H, CH), 4.93 (brs, 1H, CH), 8.71 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=8.5 (CH_3), 8.6

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(CH_3), 13.8 (CH_3), 13.9 (CH_3), 22.5 (CH_2), 28.3 (CH_3), 28.4 (CH_3), 50.4 (C), 52.8 (CH_3), 54.0 (CH_3), 55.4 (CH_3), 56.9 (CH), 57.2 (CH), 61.9 (CH_2), 146.2 (C), 146.3 (C), 150.9 (C), 151.5 (C), 151.7 (C), 168.4 (C), 168.6 (C), 169.0 (C), 169.2 (C), 169.4 (C), 169.6 (C); IR (Nujol): ν_{max}=3361, 3222, 1768, 1720, 1689 cm^{-1}; MS *m/z* (%): 556 (M^+) (6), 525 (35), 493 (46), 465 (53), 420 (44), 392 (100); anal. calcd for $C_{22}H_{32}N_6O_{11}$ (556.5233): C 47.48, H 5.80, N 15.10; found: C 47.50, H 5.81, N 15.12.

*4.3.5. Ethyl 2-[2-(5-{1-(ethoxycarbon yl)-2-[(ethoxycarbonyl)hydrazono]propyl}-1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-3-methoxy-1-methyl-3-oxopropylidene]hydrazinecarboxylate (**3u**).* Yield: 554.2 mg (97%). White powder, mp: 191–192 °C, ^{1}H NMR (400 MHz, DMSO-d_6), δ=1.12–1.21 (m, 9H, 3OCH$_2$*Me*), 1.79 (s, 3H, Me), 1.80 (s, 3H, Me), 3.04 (s, 3H, NMe), 3.07 (s, 3H, NMe), 3.61 (s, 3H, OMe), 4.06–4.12 (m, 6H, 3O*CH*$_2$Me), 4.56 (brs, 1H, CH), 4.63 (brs, 1H, CH), 9.96 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=13.7 (CH_3), 14.5 (CH_3), 17.2 (CH_3), 17.3 (CH_3), 26.3 (CH_3), 28.2 (CH_3), 52.5 (CH_3), 55.9 (CH), 56.2 (CH), 56.5 (C), 60.5 (CH_2), 61.3 (CH_2), 147.4 (C), 151.2 (C), 153.7 (C), 167.8 (C), 168.8 (C), 169.0 (C), 169.4 (C); IR (Nujol): ν_{max}=3370, 3220, 1770, 1710, 1683 cm^{-1}; MS *m/z* (%): 570 (M^+) (2), 525 (6), 479 (16), 452 (31), 420 (17), 392 (61), 347 (57); anal. calcd for $C_{23}H_{34}N_6O_{11}$ (570.5499): C 48.42, H 6.01, N 14.73; found: C 48.41, H 6.00, N 14.71.

4.4. General procedure for the synthesis of symmetrical spirobarbiturate-pyridines 4a–p and unsymmetrical spirobarbiturate-pyridines 4q–u

To a magnetically stirred solution of bis-hydrazones **3a–u** (1.0 mmol) in CH_2Cl_2 (6.0 mL), 0.15 equiv of TFA were added. The mixture was stand in these conditions for 12.0–18.0 h, until the disappearance of the **3** (TLC monitoring). The crude mixture was purified by column chromatography on silica gel to afford the products **4** that were crystallized from diethyl ether-light petroleum (bp 40–60 °C).

*4.4.1. Dimethyl 9-[(tert-butoxycarbonyl)amino]-2,4,8,10-tetramethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4a**).* Yield: 479.1 mg (100%). White powder, mp: 187–188 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.50 (9H, s, OCMe$_3$), 2.30 (s, 6H, 2Me), 3.32 and 3.33 (2s, 6H, 2NMe), 3.61 and 3.63 (2s, 6H, 2OMe), 7.73 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=15.9 (CH_3), 16.4 (CH_3), 28.1 (CH_3), 28.8 (CH_3), 51.8 (CH_3), 53.2 (C), 82.3 (C), 83.5 (C), 104.5 (C) 150.1 (C), 150.5 (C), 151.8 (C), 153.8 (C), 166.7 (C), 171.9 (C), 173.7 (C); IR (Nujol): ν_{max}=3162, 1758, 1726, 1686, 1658 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{21}H_{29}N_4O_9$: 481.1929; found: 481.1926; MS *m/z* (%): 480 (M^+) (16), 380 (48), 348 (24), 321 (14), 305 (17), 293 (82), 289 (100), 265 (24), 250 (49); anal. calcd for $C_{21}H_{28}N_4O_9$ (480.4686): C 52.50, H 5.87, N 11.66; found: C 52.48, H 5.89, N 11.63.

*4.4.2. Diethyl 9-[(tert-butoxycarbonyl)amino]-2,4,8,10-tetramethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4b**).* Yield: 324.8 mg (64%). White powder, mp: 186–188 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.42 (t, *J*=7.2 Hz, 6H, 2OCH$_2$*Me*), 1.48 and 1.52 (2s, 9H, OCMe$_3$), 2.30 (s, 6H, 2Me), 3.29 and 3.31 (2s, 6H, 2NMe), 4.02–4.10 (m, 4H, 2O*CH*$_2$Me), 7.96 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=13.9 (CH_3), 15.8 (CH_3), 16.3 (CH_3), 28.1 (CH_3), 28.7 (CH_3), 54.5 (C), 61.0 (CH_2), 82.1 (C), 83.4 (C), 104.3 (C), 150.0 (C), 150.4 (C), 151.8 (C), 153.9 (C), 154.2 (C), 166.1 (C), 171.9 (C), 173.9 (C); IR (Nujol): ν_{max}=3287, 1760, 1739, 1714, 1688, 1663 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{23}H_{33}N_4O_9$: 509.2242; found: 509.2242; MS *m/z* (%): 508 (M^+) (9), 408 (28), 334 (53), 307 (46), 290 (100), 275 (21), 250 (19), 219 (21), 204 (40); anal. calcd for $C_{23}H_{32}N_4O_9$ (508.5217): C 54.32, H 6.34, N 11.02; found: C 54.30, H 6.33, N 11.04.

*4.4.3. Dimethyl 9-[(tert-butoxycarbonyl)amino]-8,10-diethyl-2,4-dimethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4c**).* Yield: 316.1 mg (62%). White powder, mp: 184–185 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.16 (t, *J*=7.2 Hz, 6H, 2CH$_2$*Me*), 1.50 (s, 9H, OCMe$_3$), 2.43–2.52 (m, 2H, *CH*$_2$Me), 2.85–2.94 (m, 2H, *CH*$_2$Me), 3.32 (s, 6H, 2NMe), 3.60 (s, 6H, 2OMe), 7.22 and 7.88 (2 brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=13.1 (CH_3), 22.8 (CH_2), 28.1 (CH_3), 28.8 (CH_3), 51.8 (CH_3), 54.4 (C), 82.6 (C), 83.9 (C), 104.3 (C), 104.9 (C), 151.9 (C), 153.8 (C), 154.7 (C), 155.2 (C), 166.3 (C), 171.9 (C), 173.1 (C); IR (Nujol): ν_{max}=3455, 3170, 1734, 1709, 1688, 1656 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{23}H_{33}N_4O_9$: 509.2242; found: 509.2241; MS *m/z* (%): 508 (M^+) (26), 421 (14), 408 (33), 392 (24), 376 (17), 361 (49), 348 (86), 317 (100), 300 (44), 278 (46); anal. calcd for $C_{23}H_{32}N_4O_9$ (508.5212): C 54.32, H 6.34, N 11.02; found: C 54.33, H 6.35, N 11.05.

*4.4.4. Dimethyl 9-[(anilinocarbonyl)amino]-2,4,8,10-tetramethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4d**).* Yield: 308.2 mg (62%). White powder, mp: 228–229 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=2.40 (s, 6H, 2Me), 3.33 (s, 3H, NMe), 3.43 (s, 3H, NMe), 3.68 (s, 6H, 2OMe), 7.12 (t, *J*=7.2 Hz, 1H$_{ar}$), 7.35 (t, *J*=7.6 Hz, 2H$_{ar}$), 7.71 (d, *J*=8.0 Hz, 2H$_{ar}$), 8.67 (s, 1H, NH), 9.45 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=15.6 (CH_3), 28.8 (CH_3), 29.2 (CH_3), 52.1 (CH_3), 53.5 (C), 106.0 (C), 120.1 (CH), 124.0 (CH), 128.8 (CH), 137.7 (C), 150.4 (C), 152.3 (C), 156.1 (C), 166.2 (C), 172.4 (C), 173.6 (C); IR (Nujol): ν_{max}=3302, 3272, 1707, 1676 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{23}H_{26}N_5O_8$: 500.1776; found: 500.1776; MS *m/z* (%): 499 (M^+) (75), 412 (25), 380 (19), 365 (17), 319 (67), 289 (75), 288 (72), 274 (56), 250 (100), 215 (35); anal. calcd for $C_{23}H_{25}N_5O_8$ (499.4735): C 55.31, H 5.05, N 14.02; found C 55.29, H 5.04, N 13.99.

*4.4.5. Dimethyl 9-[(aminocarbonyl)amino]-2,4,8,10-tetramethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4e**).* Yield: 267.1 mg (63%). White powder, mp: 250–251 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=2.36 (s, 6H, 2Me), 3.31 (s, 3H, NMe), 3.35 (s, 3H, NMe), 3.67 (s, 6H, 2OMe), 5.20 and 7.06 (2s, 2H, NH_2), 8.66 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=15.6 (CH_3), 28.9 (CH_3), 29.1 (CH_3), 52.1 (CH_3), 53.8 (C), 106.1 (C), 150.0 (C), 151.4 (C), 159.0 (C), 166.3 (C), 172.5 (C), 173.5 (C); IR (Nujol): ν_{max}=3381, 3313, 3174, 1726, 1674, 1650 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{17}H_{22}N_5O_8$: 424.1463; found: 424.1461; MS *m/z* (%): 423 (M^+) (12), 390 (17), 379 (16), 334 (100), 319 (21), 290 (100), 279 (42); anal. calcd for $C_{17}H_{21}N_5O_8$ (423.3775): C 48.23, H 5.00, N 16.54; found: C 48.21, H 4.99, N 16.57.

*4.4.6. Diethyl 9-[(aminocarbonyl)amino]-2,4,8,10-tetramethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4f**).* Yield: 277.1 mg (62%). White powder, mp: 178–180 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.19 (t, *J*=7.2 Hz, 6H, 2OCH$_2$*Me*), 2.36 (s, 6H, 2Me), 3.29 and 3.33 (2s, 6H, 2NMe), 4.04–4.16 (m, 4H, 2O*CH*$_2$Me), 5.21 and 7.05 (2 brs, 2H, NH_2), 8.64 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=13.9 (CH_3), 15.4 (CH_3), 28.8 (CH_3), 29.0 (CH_3), 53.7 (C), 61.4 (CH_2), 106.1 (C), 149.8 (C), 151.4 (C), 159.0 (C), 165.7 (C), 172.4 (C), 173.6 (C); IR (Nujol): ν_{max}=3414, 3348, 1744, 1724, 1663, 1617 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{19}H_{26}N_5O_8$: 452.1776; found: 452.1775; MS *m/z* (%): 451 (M^+) (12), 406 (10), 350 (26), 333 (100), 308 (16), 289 (14), 274 (30); anal. calcd for $C_{19}H_{25}N_5O_8$ (451.4307): C 50.55, H 5.58, N 15.51; found: C 50.53, H 5.57, N 15.49.

4.4.7. Dimethyl 9-[(anilinocarbonyl)amino]-2,4-diethyl-8,10-dimethyl-1,5-dioxo-3-thioxo-2,4,9-triazaspiro[5.5]undeca-7,10-

*diene-7,11-dicarboxylate (**4g**).* Yield: 431.9 mg (96%). White powder, mp: 190–192 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.22 (t, J=7.2 Hz, 3H, NCH_2Me), 1.31 (t, J=7.2 Hz, 3H, NCH_2Me), 2.42 (s, 6H, 2Me), 3.66 (s, 6H, 2OMe), 4.46 (d, J=6.8 Hz, 2H, NCH_2Me), 4.59 (d, J=7.2 Hz, 2H, NCH_2Me), 7.13 (t, J=7.2 Hz, 1H$_{ar}$), 7.36 (t, J=7.2 Hz, 2H$_{ar}$), 7.72 (d, J=7.6 Hz, 2H$_{ar}$), 8.62 (s, 1H, NH), 9.27 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=11.8 (CH_3), 15.2 (CH_3), 15.5 (CH_3), 44.0 (CH_2), 52.3 (CH_3), 53.6 (C), 106.9 (C), 120.1 (CH), 124.0 (CH), 128.8 (CH), 137.8 (C), 150.0 (C), 156.0 (C), 165.8 (C), 170.6 (C), 172.0 (C), 179.2 (C); IR (Nujol): ν_{max}=3313, 1734, 1722, 1686, 1666, 1654 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{25}H_{30}N_5O_7S$: 544.1860; found: 544.1862; MS m/z (%): 543 (M$^+$) (16), 385 (100), 370 (40), 334 (30), 290 (100), 279 (30), 264 (40), 250 (100); anal. calcd for $C_{25}H_{29}N_5O_8S$ (543.5933): C 55.24, H 5.38, N 12.88; found: C 55.22, H 5.39, N 12.90.

*4.4.8. Diethyl 9-[(anilinocarbonyl)amino]-2,4-diethyl-8,10-dimethyl-1,5-dioxo-3-thioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4h**).* Yield: 479.6 mg (84%). White powder, mp: 181–183 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.20–1.26 (m, 9H, NCH_2Me and 2 OCH_2Me), 1.32 (t, J=7.2 Hz, 3H, NCH_2Me), 2.41 (s, 6H, 2Me), 4.02–4.08 (m, 2H, OCH_2Me), 4.18–4.23 (m, 2H, OCH_2Me), 4.45 (q, J=6.8 Hz, 2H, NCH_2Me), 4.57 (q, J=6.8 Hz, 2H, NCH_2Me), 7.13 (t, J=7.6 Hz, 1H$_{ar}$), 7.36 (t, J=7.2 Hz, 2H$_{ar}$), 7.74 (d, J=7.6 Hz, 2H$_{ar}$), 8.72 (s, 1H, NH), 8.92 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=11.5 (CH_3), 11.9 (CH_3), 14.0 (CH_3), 15.5 (CH_3), 26.9 (CH_3), 44.0 (CH_2), 44.2 (CH_2), 53.5 (C), 61.4 (CH), 107.2 (C), 120.1 (CH), 124.0 (CH), 128.9 (CH), 137.8 (C), 149.3 (C), 156.0 (C), 165.5 (C), 170.5 (C), 172.1 (C), 179.2 (C); IR (Nujol): ν_{max}=3326, 3193, 1724, 1688, 1672 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{27}H_{34}N_5O_7S$: 572.2173; found: 572.2173; MS m/z (%): 571 (M$^+$) (9), 453 (16), 413 (38), 384 (100), 250 (26), 204 (51); anal. calcd for $C_{27}H_{33}N_5O_7S$ (571.6464): C 56.73, H 5.82, N 12.25; found: C 56.71, H 5.81, N 12.27.

*4.4.9. Diisopropyl 9-[(anilinocarbonyl)amino]-2,4-diethyl-8,10-dimethyl-1,5-dioxo-3-thioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4i**).* Yield: 431.9 mg (72%). White powder, mp: 181–182 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.17–1.25 (m, 15H, $2OCHMe_2$ and NCH_2Me), 1.33 (t, J=7.2 Hz, 3H, NCH_2Me), 2.39 (s, 6H, 2Me), 4.45 (d, J=7.2 Hz, 2H, NCH_2Me), 4.56 (d, J=7.2 Hz, 2H, NCH_2Me), 5.00 (hept, J=6.4 Hz, 2H, $OCHMe_2$), 7.12 (t, J=7.6 Hz, 1H$_{ar}$), 7.36 (t, J=7.6 Hz, 2H$_{ar}$), 7.76 (d, J=7.6 Hz, 2H$_{ar}$), 8.74 (s, 1H, NH), 9.23 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=11.4 (CH_3), 12.0 (CH_3), 15.6 (CH_3), 21.5 (CH_3), 21.8 (CH_3), 44.0 (CH_2), 44.2 (CH_2), 53.6 (C), 69.3 (CH), 107.4 (C), 120.0 (CH), 123.8 (CH), 128.8 (CH), 138.0 (C), 148.9 (C), 156.2 (C), 165.4 (C), 170.6 (C), 172.2 (C), 179.3 (C); IR (Nujol): ν_{max}=3361, 3186, 1722, 1674, 1686 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{29}H_{38}N_5O_7S$: 600.2486; found: 600.2486; MS m/z (%): 599 (M$^+$) (1), 436 (7), 421 (5), 334 (72), 290 (100), 279 (24), 264 (18); anal. calcd for $C_{29}H_{37}N_5O_7S$ (599.6996): C 58.08, H 6.22, N 11.68; found: C 58.10, H 6.21, N 11.69.

*4.4.10. Di-tert-butyl 9-[(anilinocarbonyl)amino]-2,4-diethyl-8,10-dimethyl-1,5-dioxo-3-thioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4j**).* Yield: 508.3 mg (81%). White powder, mp: 180–181 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.26 (t, J=7.2 Hz, 3H, NCH_2Me), 1.33 (t, J=6.8 Hz, 3H, NCH_2Me), 1.41 and 1.43 (2s, 18H, $2OCMe_3$), 2.35 (s, 6H, 2Me), 4.43 (q, J=7.2 Hz, 2H, NCH_2Me), 4.58 (q, J=6.8 Hz, 2H, NCH_2Me), 7.12 (t, J=7.6 Hz, 1H$_{ar}$), 7.37 (t, J=8.0 Hz, 2H$_{ar}$), 7.79 (d, J=7.6 Hz, 2H$_{ar}$), 8.87 (s, 1H, NH), 9.25 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=11.5 (CH_3), 11.9 (CH_3), 15.6 (CH_3), 26.9 (CH_3), 28.1 (CH_3), 44.1 (CH_2), 44.2 (CH_2), 53.6 (C), 82.5 (C), 108.2 (C), 119.9 (CH), 123.7 (CH), 128.8 (CH), 138.2 (C), 147.7 (C), 156.4 (C), 165.3 (C), 170.6 (C), 172.2 (C), 179.5 (C); IR (Nujol): ν_{max}=3425, 3306, 1729, 1688, 1605 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{31}H_{42}N_5O_7S$: 628.2799; found: 628.2798; MS m/z (%): 627 (M$^+$) (30), 582 (10), 471 (29), 427 (25), 357 (100), 311 (28); anal. calcd for $C_{31}H_{41}N_5O_7S$ (627.7527): C 59.31, H 6.58, N 11.16; found: C 59.33, H 6.58, N 11.19.

*4.4.11. Diallyl 9-[(anilinocarbonyl)amino]-2,4-diethyl-8,10-dimethyl-1,5-dioxo-3-thioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4k**).* Yield: 369.1 mg (62%). White powder, mp: 178–180 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.23 (t, J=7.2 Hz, 3H, NCH_2Me), 1.31 (t, J=6.8 Hz, 3H, NCH_2Me), 2.44 (s, 6H, 2Me), 4.39–4.50 (m, 6H, NCH_2Me and OAllyl), 4.56 (q, J=6.8 Hz, 2H, NCH_2Me), 5.23–5.30 (m, 4H, OAllyl), 5.77–5.87 (m, 2H, OAllyl), 7.13 (t, J=7.6 Hz, 1H$_{ar}$), 7.37 (t, J=7.6 Hz, 2H$_{ar}$), 7.74 (d, J=7.6 Hz, 2H$_{ar}$), 8.70 (brs, 1H, NH), 9.57 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=11.5 (CH_3), 11.9 (CH_3), 15.5 (CH_3), 26.8 (CH_2), 44.1 (CH_2), 53.5 (C), 66.1 (CH_2), 106.8 (C), 119.6 (C), 120.0 (CH), 123.9 (CH), 128.8 (CH), 131.1 (CH), 137.8 (C), 149.9 (C), 156.2 (C), 165.1 (C), 170.5 (C), 172.0 (C), 179.1 (C); IR (Nujol): ν_{max}=3310, 3219, 1720, 1687, 1662 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{29}H_{34}N_5O_7S$: 596.2173; found: 596.2173; MS m/z (%): 595 (M$^+$) (4), 476 (9), 452 (8), 396 (100), 303 (12), 262 (16), 204 (13); anal. calcd for $C_{29}H_{33}N_5O_7S$ (595.6678): C 58.47, H 5.58, N 11.76; found: C 58.45, H 5.59, N 11.78.

*4.4.12. Diethyl 9-[(aminocarbonyl)amino]-2,4-diethyl-8,10-dimethyl-1,5-dioxo-3-thioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4l**).* Yield: 336.4 mg (68%). White powder, mp: 186–187 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.17–1.25 (m, 12H, $2NCH_2Me$ and 2 OCH_2Me), 2.35 (s, 6H, 2Me), 3.96–4.04 (m, 2H, OCH_2Me), 4.12–4.20 (m, 2H, OCH_2Me), 4.38–4.49 (m, 4H, $2NCH_2Me$), 5.24 and 7.00 (2 brs, 2H, NH_2), 8.71 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=11.8 (CH_3), 12.2 (CH_3), 14.3 (CH_3), 15.6 (CH_3), 44.2 (CH_2), 54.0 (C), 61.6 (CH_2), 107.1 (C), 149.5 (C), 159.4 (C), 165.8 (C), 170.9 (C), 172.1 (C), 179.6 (C); IR (Nujol): ν_{max}=3315, 3221, 1719, 1690, 1662 cm^{-1}; MS m/z (%): 495 (M$^+$) (5), 466 (38), 449 (47), 421 (73), 393 (14), 377 (68), 348 (100); anal. calcd for $C_{21}H_{29}N_5O_7S$ (495.5505): C 50.90, H 5.90, N 14.13; found: C 50.92, H 5.89, N 14.16.

*4.4.13. Dimethyl 9-[(anilinocarbonyl)amino]-2,4-dicyclohexyl-8,10-dimethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4m**).* Yield: 387.6 mg (61%). White powder, mp: 186–187 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.20–1.43 (m, 6H, Cyclohexyl), 1.62–1.88 (m, 10H, Cyclohexyl), 2.24–2.40 (2m, 4H, Cyclohexyl), 2.36 (s, 6H, 2Me), 3.66 (s, 6H, 2OMe), 4.61 (t, J=3.6 Hz, 1H, Cyclohexyl), 4.72 (t, J=3.6 Hz, 1H, Cyclohexyl), 7.12 (t, J=7.2 Hz, 1H$_{ar}$), 7.34 (t, J=7.6 Hz, 2H$_{ar}$), 7.77 (d, J=7.6 Hz, 2H$_{ar}$), 8.79 (s, 1H, NH), 9.03 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=15.4 (CH_3), 25.2 (CH_2), 25.5 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.9 (CH_2), 28.5 (CH_2), 28.8 (CH_2), 51.9 (C), 54.0 (C), 55.6 (CH), 56.2 (CH), 106.7 (C), 120.2 (CH), 124.0 (CH), 128.7 (CH), 137.8 (C), 149.3 (C), 150.9 (C), 156.1 (C), 166.0 (C), 172.1 (C), 173.8 (C); IR (Nujol): ν_{max}=3315, 3222, 1730, 1691, 1660 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{33}H_{42}N_5O_8$: 636.3028; found: 636.3026; MS m/z (%): 635 (M$^+$) (15), 500 (21), 418 (16), 385 (70), 370 (39), 299 (36), 250 (100); anal. calcd for $C_{33}H_{41}N_5O_8$ (635.7075): C 62.35, H 6.50, N 11.02; found: C 62.33, H 6.49, N 11.04.

*4.4.14. Diethyl 9-[(anilinocarbonyl)amino]-2,4-dicyclohexyl-8,10-dimethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4n**).* Yield: 484.7 mg (73%). White powder, mp: 181–182 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.22–1.43 (m, 12H, $2OCH_2Me$ and Cyclohexyl), 1.62–1.87 (m, 10H, Cyclohexyl), 2.23–2.36 (m, 4H, Cyclohexyl), 2.35 (s, 6H, 2Me), 4.00–4.08 (2m, 2H, OCH_2Me), 4.20–4.25 (m, 2H, OCH_2Me), 4.61 (t, J=3.6 Hz, 1H, Cyclohexyl), 4.73 (t, J=3.6 Hz, 1H, Cyclohexyl), 7.12 (t, J=7.2 Hz, 1H$_{ar}$), 7.35 (t, J=7.6 Hz, 2H$_{ar}$), 7.79 (d, J=7.6 Hz, 2H$_{ar}$), 8.40 (s, 1H, NH), 8.88 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), 14.1 (CH_3), 15.6 (CH_3), 25.3 (CH_2), 25.6 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.9 (CH_2), 28.5

(CH_2), 28.8 (CH_2), 54.1 (C), 55.9 (CH), 56.3 (CH), 61.3 (CH_2), 107.1 (C), 120.2 (CH), 124.0 (CH), 128.8 (CH), 138.0 (C), 148.5 (C), 151.0 (C), 155.8 (C), 165.9 (C), 172.1 (C), 173.8 (C); IR (Nujol): ν_{max}=3318, 3221, 1730, 1685, 1662 cm^{-1}; MS *m*/*z* (%): 663 (M^+) (10), 619 (8), 545 (15), 528 (9), 413 (29), 384 (100), 278 (34); anal. calcd for $C_{35}H_{45}N_5O_8$ (663.7607): C 63.33, H 6.83, N 10.55; found: C 63.31, H 6.85, N 10.57.

*4.4.15. Diallyl 9-[(anilinocarbonyl)amino]-2,4-dicyclohexyl-8,10-dimethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4o**).* Yield: 447.3 mg (65%). White powder, mp: 181–182 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.26–1.43 (m, 6H, Cyclohexyl), 1.62–1.87 (m, 10H, Cyclohexyl), 2.21–2.35 (m, 4H, Cyclohexyl), 2.38 (s, 6H, 2Me), 4.44–4.50 (m, 4H, OAllyl), 4.60 (t, *J*=3.6 Hz, 1H, Cyclohexyl), 4.67–4.72 (m, 5H, Cylohexyl and OAllyl), 5.81–5.88 (m, 2H, OAllyl), 7.14 (t, *J*=7.2 Hz, $1H_{ar}$), 7.35 (t, *J*=7.2 Hz, $2H_{ar}$), 7.81 (d, *J*=8 Hz, $2H_{ar}$), 8.81 (s, 1H, NH), 8.98 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=15.7 (CH_3), 25.3 (CH_2), 25.6 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 28.6 (CH_2), 28.8 (CH_2), 54.2 (C), 55.9 (CH), 56.3 (CH), 66.0 (CH_2), 106.8 (C), 119.2 (CH_2), 120.0 (CH), 123.8 (CH), 128.7 (CH), 131.3 (CH), 138.1 (C), 149.0 (C), 151.0 (C), 155.9 (C), 165.6 (C), 172.0 (C), 173.7 (C); IR (Nujol): ν_{max}=3321, 3210, 1725, 1688, 1659 cm^{-1}; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{37}H_{46}N_5O_8$: 688.3341; found: 688.3341; MS *m*/*z* (%): 687 (M^+) (3), 574 (13), 552 (9), 470 (8), 434 (9), 396 (100), 303 (14), 262 (18), 219 (20), 204 (28); anal. calcd for $C_{37}H_{45}N_5O_8$ (687.7821): C 64.61, H 6.59, N 10.18; found: C 64.59, H 6.60, N 10.21.

*4.4.16. Dimethyl 9-[(anilinocarbonyl)amino]-2,4-dicyclohexyl-8,10-diethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4p**).* Yield: 480.1 mg (72%). White powder, mp: 178–180 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.17–1.42 (m, 12H, $2CH_2$*Me* and Cyclohexyl), 1.59–1.82 (2m, 10H, Cyclohexyl), 2.04–2.35 (m, 6H, Cyclohexyl and *CH*$_2$Me), 2.81–2.86 (m, 2H, *CH*$_2$Me), 3.65 (s, 6H, 2OMe), 4.58 (t, *J*=3.6 Hz, 1H, Cyclohexyl), 4.71 (t, *J*=3.6 Hz, 1H, Cyclohexyl), 7.09 (t, *J*=7.2 Hz, $1H_{ar}$), 7.31 (t, *J*=7.6 Hz, $2H_{ar}$), 7.76 (d, *J*=8 Hz, $2H_{ar}$), 7.97 (s, 1H, NH), 8.88 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=13.2 (CH_3), 22.4 (CH_2), 25.3 (CH_2), 25.5 (CH_2), 26.4 (CH_2), 26.9 (CH_2), 28.5 (CH_2), 28.8 (CH_2), 51.9 (CH_3), 53.6 (C), 55.7 (CH), 56.3 (CH), 106.7 (C), 120.3 (CH), 123.9 (CH), 128.7 (CH), 138.0 (C), 151.0 (C), 153.9 (C), 155.6 (C), 165.8 (C), 171.7 (C), 173.8 (C); IR (Nujol): ν_{max}=3220, 3190, 1721, 1685, 1650 cm^{-1}; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{35}H_{46}N_5O_8$: 664.3341; found: 664.3341; MS *m*/*z* (%): 663 (M^+) (3), 571 (18), 539 (27), 512 (48), 481 (56), 453 (100); anal. calcd for $C_{35}H_{45}N_5O_8$ (663.7607): C 63.33, H 6.83, N 10.55; found: C 63.32, H 5.82, N 10.56.

*4.4.17. Ethyl methyl 9-[(tert-butoxycarbonyl)amino]-2,4,8,10-tetramethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4q**).* Yield: 500.1 mg (91%). White powder, mp 191–193 °C, ^{1}H NMR (400 MHz, DMSO-d_6), δ=1.04 (t, *J*=7.2 Hz, 3H, OCH_2*Me*), 1.44 (s, 9H, $OCMe_3$), 2.13 (s, 3H, Me), 2.17 (s, 3H, Me), 3.13 and 3.14 (2s, 6H, 2NMe), 3.54 (s, 3H, OMe), 3.97 (q, *J*=7.2 Hz, 2H, O*CH*$_2$Me), 10.04 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=13.5 (CH_3), 15.5 (CH_3), 15.8 (CH_3), 27.8 (CH_3), 28.4 (CH_3), 52.0 (CH_3), 54.2 (C), 60.7 (CH_2), 81.1 (C), 103.0 (C), 103.1 (C), 149.3 (C), 149.7 (C), 151.3 (C), 154.5 (C), 165.6 (C), 166.5 (C), 171.8 (C); IR (Nujol): ν_{max}=3330, 3215, 1728, 1695 cm^{-1}; MS *m*/*z* (%): 494 (M^+) (2), 420 (63), 393 (41), 390 (17), 361 (74), 317 (51), 289 (87); anal. calcd for $C_{22}H_{30}N_4O_9$ (494.4952): C 53.44, H 6.11, N 11.33; found: C 53.42, H 6.10, N 11.35.

*4.4.18. 11-Ethyl 7-methyl 9-[(tert-butoxycarbonyl)amino]-8-ethyl-2,4,10-trimethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4r**).* Yield: 467.6 mg (92%). White powder, mp 182–184 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.11–1.20 (m, 6H, CH_2*Me* and OCH_2*Me*), 1.45 and 1.50 (2s, 9H, $OCMe_3$), 2.32 (s, 3H, Me), 2.52–2.58 and 2.82–2.89 (2m, 2H, *CH*$_2$Me), 3.30 and 3.33 (2s, 6H, 2NMe), 3.61 (s, 3H, OMe), 4.03–4.10 (m, 2H, O*CH*$_2$Me), 7.37 and 7.46 (2brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=13.0 (CH_3), 13.8 (CH_3), 15.8 (CH_3), 23.0 (CH_2), 28.1 (CH_3), 28.8 (CH_3), 51.9 (CH_3), 54.5 (C), 61.0 (CH_2), 82.5 (C), 83.7 (C), 104.2 (C), 104.9 (C), 150.3 (C), 151.9 (C), 153.8 (C), 155.1 (C), 166.1 (C), 166.4 (C), 172.0 (C), 173.4 (C); IR (Nujol): ν_{max}=3330, 3251, 1725, 1686 cm^{-1}; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{23}H_{33}N_4O_9$: 509.2242; found: 509.2243; MS *m*/*z* (%): 508 (M^+) (4), 434 (71), 389 (100), 330 (82); anal. calcd for $C_{23}H_{32}N_4O_9$ (508.5217): C 54.32, H 6.34, N 11.02; found: C 54.35, H 6.32, N 11.05.

*4.4.19. Ethyl isopropyl 9-[(tert-butoxycarbonyl)amino]-2,4,8,10-tetramethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4s**).* Yield: 444.2 mg (85%). White powder, mp: 177–179 °C, ^{1}H NMR (400 MHz, DMSO-d_6), δ=1.01–1.06 (m, 9H, $OCHMe_2$ and OCH_2*Me*), 1.44 (s, 9H, $OCMe_3$), 2.13, 2.15 and 2.16 (3s, 6H, 2Me), 3.12, 3.13 and 3.14 (3s, 6H, 2NMe), 3.94–4.01 (m, 2H, O*CH*$_2$Me), 4.82 (hept, *J*=6.4 Hz, 1H, O*CH*Me$_2$), 10.01 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=14.2 (CH_3), 16.1 (CH_3), 16.2 (CH_3), 21.7 (CH_3), 28.6 (CH_3), 29.6 (CH_3), 54.7 (CH), 61.4 (CH_2), 68.8 (CH), 81.7 (C), 103.7 (C), 149.8 (C), 150.1 (C), 152.0 (C), 155.2 (C), 165.6 (C), 166.4 (C), 172.4 (C), 172.8 (C); IR (Nujol): ν_{max}=3329, 3201, 1724, 1690, 1658 cm^{-1}; MS *m*/*z* (%): 522 (M^+) (3), 478 (2), 448 (15), 421 (5), 393 (4); anal. calcd for $C_{24}H_{34}N_4O_9$ (522.5483): C 55.16, H 6.56, N 10.72; found: C 55.19, H 6.55, N 10.74.

*4.4.20. 11-Ethyl 7-methyl 8-ethyl-9-[(methoxycarbonyl)amino]-2,4,10-trimethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4t**).* Yield: 387.2 mg (83%). White powder, mp: 175–177 °C, ^{1}H NMR (400 MHz, $CDCl_3$), δ=1.04–1.08 (m, 3H, CH_2*Me*), 1.12 (t, *J*=7.2 Hz, 3H, OCH_2*Me*), 2.26 (s, 3H, Me), 2.42–2.50 and 2.78–2.85 (2m, 2H, *CH*$_2$Me), 3.27 and 3.29 (2s, 6H, 2NMe), 3.58 (s, 3H, OMe), 3.78 and 3.82 (2s, 3H, OMe), 4.00–4.07 (m, 2H, O*CH*$_2$Me), 8.11 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ=12.7 (CH_3), 12.8 (CH_3), 13.7 (CH_3), 15.6 (CH_3), 16.0 (CH_3), 22.9 (CH_3), 28.8 (CH_3), 51.9 (CH_3), 53.5 (CH_3), 53.9 (CH), 61.1 (CH_2), 104.3 (C), 104.9 (C), 149.9 (C), 150.2 (C), 151.7 (C), 154.4 (C), 154.9 (C), 155.6 (C), 156.2 (C), 166.0 (C), 166.4 (C), 171.8 (C), 172.3 (C), 173.1 (C), 173.4 (C); IR (Nujol): ν_{max}=3331, 3221, 1715, 1693, 1654 cm^{-1}; MS *m*/*z* (%): 466 (M^+) (12), 436 (6), 407 (10), 379 (16), 362 (100); anal. calcd for $C_{20}H_{26}N_4O_9$ (466.4420): C 51.50, H 5.62, N 12.01; found: C 51.51, H 5.63, N 12.04.

*4.4.21. Ethyl methyl 9-[(ethoxycarbonyl)amino]-2,4,8,10-tetramethyl-1,3,5-trioxo-2,4,9-triazaspiro[5.5]undeca-7,10-diene-7,11-dicarboxylate (**4u**).* Yield: 387.3 mg (83%). White powder, mp: 188–190 °C, ^{1}H NMR (400 MHz, DMSO-d_6), δ=1.05 (t, *J*=6.8 Hz, 3H, OCH_2*Me*), 1.23 (t, *J*=6.8 Hz, 3H, OCH_2*Me*), 2.15 and 2.17 (2s, 3H, Me), 2.19 and 2.22 (2s, 3H, Me), 3.15 (s, 3H, NMe), 3.16 (s, 3H, NMe), 3.56 (s, 3H, OMe), 3.98 (q, *J*=6.8 Hz, 2H, O*CH*$_2$Me), 4.16 (q, *J*=6.8 Hz, 2H, O*CH*$_2$Me), 10.29 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ=13.5 (CH_3), 14.4 (CH_3), 15.5 (CH_3), 15.7 (CH_3), 28.4 (CH_3), 52.0 (CH_3), 54.2 (C), 103.1 (C), 103.2 (C), 149.2 (C), 149.6 (C), 151.3 (C), 155.0 (C), 165.5 (C), 166.5 (C), 171.8 (C), 172.1 (C); IR (Nujol): ν_{max}=3328, 3218, 1720, 1689, 1648 cm^{-1}; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{27}N_4O_9$: 467.1773; found: 467.1770; MS *m*/*z* (%): 466 (M^+) (3), 421 (16), 393 (12), 376 (27), 348 (44), 317 (51), 289 (100); anal. calcd for $C_{20}H_{26}N_4O_9$ (466.4420): C 51.50, H 5.62, N 12.01; found: C 51.48, H 5.63, N 12.03.

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