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Bis-heterocycles. Part I: tetrahydro-5,5′-bi(1,2,4-triazin-6-ones)

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Abstract: Selected sets of tetrahydro-5,5′-bi(1,2,4-triazines) (**1–3**) appended with acetyl, benzoyl, and ester moieties at C-3 position and *N*-1 (*p*-substituted)phenyl ring have been prepared and characterized by spectral (IR, NMR, MS) data and X-ray diffraction for compound **3a**. Their synthesis was achieved in high yield via the reaction of diethyl aminomalonate with various *N*-(aryl)hydrazonoyl chlorides in the presence of triethylamine.

Keywords: diethyl aminomalonate; dihydro-1,2,4-triazin-6-ones; hydrazonoyl chlorides; oxidative dimerization; X-ray crystal structure.

1 Introduction

1,2,4-Triazine entity, fused to pyrimidine-2,4-diones, is found in a class of naturally occurring antibiotics, for example, reumycin [1]. The chemistry of 1,2,4-triazines has been well documented [2, 3]. Several of their derivatives exhibited remarkable biological activity such as antagonist receptor at the corticotropin-releasing factor [4], anti-HIV [5], and anticancer activity [5, 6]. Besides, synthetic procedures for various 5,5′-bi(1,2,4-triazines), exemplified in Fig. 1, have been published [7–10]; their herbicidal activity [9] and use as bidentate nitrogen ligands in metallosupramolecular chemistry [10] have also been reported.

In the 1990s, we became interested in the chemistry of triazines and had the occasion to develop a facile method toward the synthesis of optically active 4,5-dihydro-1,2,4-triazin-6-ones [11–13]. Recently, we have also reported on a novel oxidative coupling of alkanones and cycloalkanones with 3-(pyridine-2-yl)-1,2,4-triazinones coordinated to Pd (II) [14, 15]. A number of reports have also recently dealt with the synthesis of 4,5-dihydro-1,2,4-triazin-6-ones [16–22], some of which have potentials as antifungal [19, 20], anticonvulsant [21], and peptidomimetic [22] agents. Interest in bis-heterocyclic systems stems from the fact that many of these dimeric compounds exhibit higher activity than their monoheterocyclic analogs. In this context, we have reported on a direct synthesis of model tetrahydro-5,5′-bi(1,2,4-triazin-6-ones) (**1a**, **b**; Fig. 1) [23]. We felt that this synthetic route and the various attainable dimeric triazinones, exemplified by compounds **1–3**, illustrated in Scheme 1 (see below), are worthy of follow-up and deserve further inspection.

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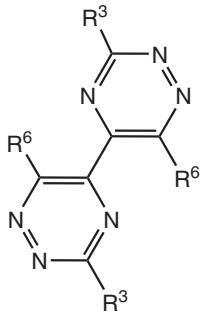
2 Results and discussion

2.1 Synthesis

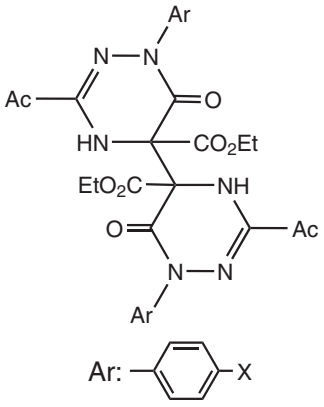
The versatile reaction of chiral α-amino esters with *N*-(aryl)hydrazonoyl chlorides (precursors of nitrile imine 1,3-dipolar species) yields the respective chiral 4,5-dihydro-1,2,4-triazin-6-ones [11]. Yet, our recent study has shown that the reaction of aminomalonic ester with *N*-(aryl)hydrazonoyl chlorides (**Ia**, **b**) yielded the respective dimeric products, namely, diethyl-l6,6′-dioxo-tetrahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylates **1a**, **b** (Fig. 1). Herein, we produce further examples, dimers **1–3**, on this novel one-pot synthesis (involving oxidative dimerization modes) with different R groups, together with various *para*-X substituents at the *N*-aromatic ring (Scheme 1).

The production of the bis-heterocycles **1–3** most logically proceeds via initiated formation of the monomeric 6-oxo-4,5-dihydro-1,2,4-triazine-5-carboxylates (**1A–3A**); the latter precursors are then transformed into **1–3**, for which a plausible radical-mediated pathway involving a single-electron transfer is postulated in Scheme 2. The instability of **1A–3A** in basic media might be due to the tendency of their resonance-stabilized enolate anions **1B–3B** to form radical species **1R–3R** by the action of oxygen in



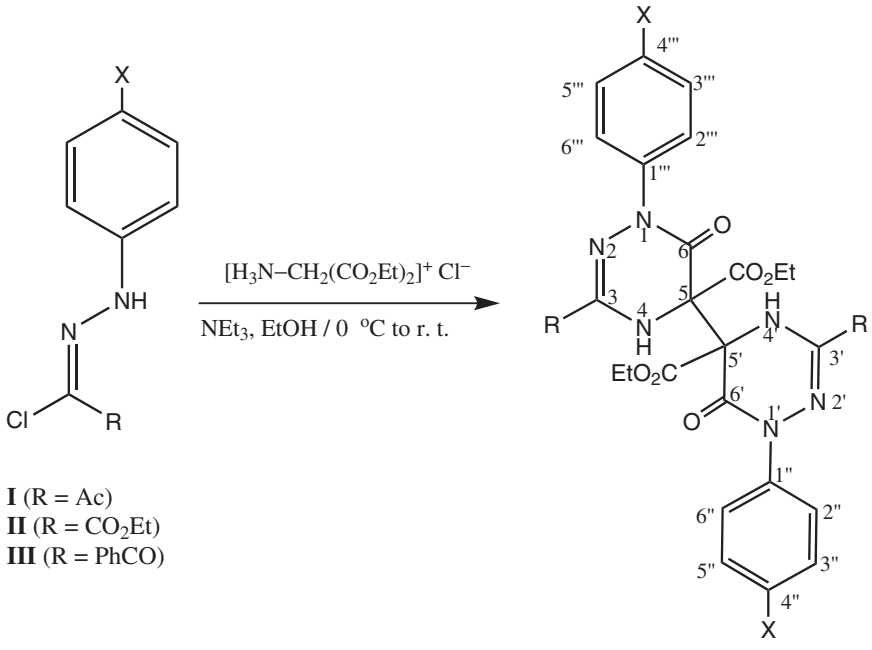
5,5'-bi(1,2,4-triazines)

R^3 = H, OMe, SMe, NH_2 / R^6 = H
R^3 = H, OMe, SMe / R^6 = Me



1a (X = Cl); **1b** (X = Br)

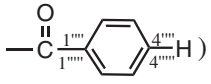
Fig. 1: Synthetic 5,5′-bi(1,2,4-triazines) and **1a, b**.



I (R = Ac)
II (R = CO_2Et)
III (R = PhCO)

Entry	a	b	c	d	e	f	g
X	Cl	Br	H	CO_2Me	Me	CN	OMe

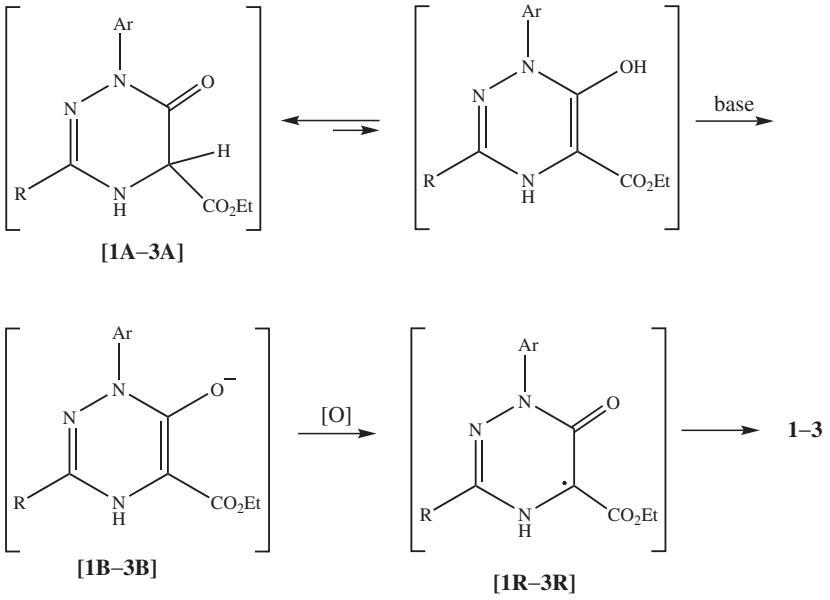
1–3

Compounds: **1c–g** (R = Ac); **2a–f** (R = CO_2Et); **3a–e** (R = )

Scheme 1: Formation of compounds **1–3**.

basic solution; the resulting carbon radicals **1R–3R** are then liable to undergo radical coupling, thereby producing the respective dimeric products **1–3** (Scheme 2). This mode of oxidative dimerization has recently been noted [23].

The newly synthesized compounds **1–3** were characterized by IR, MS, ^{1}H, and ^{13}C NMR spectral data. These data, detailed in the Experimental Section, are consistent with the suggested structures. Thus, the mass spectra display the correct molecular ion peaks for which the measured high-resolution mass spectra (HRMS) data are in good agreement with the calculated values. Distortionless enhancement of polarization transfer and 2D (correlation spectroscopy, heteronuclear multiple quantum coherence, heteronuclear multiple



Scheme 2: Proposed mechanism for the formation of the dimeric compounds **1–3**.

bond correlation) experiments showed correlations that helped in the ^{1}H and ^{13}C signal assignments to the different carbons and their attached and/or neighboring hydrogen atoms. Notably, the ^{1}H and ^{13}C NMR spectra of the reaction products lack the methine H-5 protons signal as well as the HC-5 cabon signal (absent in DEPT experiments) that are characteristic of the monomeric dihyro-1,2,4-triazinnes. Conversely, the ^{13}C NMR spectra displayed a low-intensity signal at $\delta \approx 65$ ppm (absent in DEPT); this signal is assigned to the equivalent quaternary hetero-ring carbons C-5/C-5′ and is diagnostic of the dimeric products **1–3**.

2.2 Crystal and molecular structure of 3a

An X-ray crystal structure determination was performed to confirm the structure of **3a** as a representative example of the new synthetic 3-benzoyl dimeric products **3a–e**. A summary of the crystal data and numbers pertinent to data collection and refinement parameters is given in Table 1. Selected bond lengths and angles are provided in Table 2. The molecular structure of **3a** is shown in Fig. 2. The compound crystallizes in space group $P\bar{1}$ with two different half-molecules in the asymmetric unit; the other two halves are generated by a center of inversion as is shown in Fig. 2 for one of the two crystallographically independent molecules. Bond distances and angles are similar in the two crystallographically independent molecules. For example, the C5–C5A bond

Table 1: Crystal data and numbers pertinent to data collection and structure refinement of **3a**.

Empirical formula	$C_{38}H_{30}Cl_2N_6O_8$
Formula weight, g mol^{-1}	769.58
Temperature, K	293 (2)
Wavelength λ, Å	0.71073
Crystal system	Triclinic
Space group	$P\bar{1}$
a, Å	9.6845 (5)
b, Å	9.8357 (5)
c, Å	19.9354 (11)
α, deg	90.587 (4)
β, deg	99.905 (4)
γ, deg	105.203 (4)
Volume, Å^3	1802.09 (16)
Z	2
Density (calcd.), g cm^{-3}	1.418
Abs. coeff. μ(MoKα), mm^{-1}	0.243
F(000), *e*	796
θ range for data collection, deg	2.90–25.00
Index ranges *hkl*	$-11 \le h \le 11$, $11 \le k \le 10$, $-23 \le l \le 19$
Reflections collected	13525
Reflections unique/R_{int}	6353/0.0261
Completeness to $\theta = 25.0°$, %	99.8
Absorption correction	Semiempirical from equivalents
Max./min. transmission	1.00000/0.90331
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6353/0/506
Final *R*1/*wR*2 [$I > 2\sigma(I)$][a,b]	0.0513/0.1109
Final *R*1/*wR*2 (all data)[a,b]	0.0889/0.1319
Goodness-of-fit[c] on F^2	1.017
Largest diff. peak/hole, *e* Å^{-3}	0.24/−0.23

[a] $R1 = \Sigma \,||F_o| - |F_c|| / \Sigma |F_o|$. [b] $wR2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\mathrm{Max}(F_o^2, 0) + 2F_c^2)/3$. [c] $\mathrm{GoF} = S = [\Sigma w(F_o^2 - F_c^2)^2 / (n_{obs} - n_{param})]^{1/2}$.

Table 2: Selected bond lengths (Å) and angles (deg) for one of the two crystallographically independent molecules of **3a**.

N(2)–N(1)	1.402(2)	C(6)–N(1)–N(2)	124.9(2)
N(2)–C(3)	1.286(3)	C(6)–N(1)–C(7)	122.2(2)
N(4)–C(3)	1.344(3)	C(3)–N(2)–N(1)	115.6(2)
N(4)–C(5)	1.439(3)	N(2)–C(3)–N(4)	126.0(2)
C(6)–C(5)	1.534(3)	N(2)–C(3)–C(13)	120.4(2)
C(6)–N(1)	1.358(3)	C(3)–N(4)–C(5)	123.6(2)
O(6)–C(6)	1.221(3)	N(4)–C(5)–C(6)	110.7(2)
N(1)–C(7)	1.436(3)	C(6)–C(5)–C(20)	107.4(2)
C(13)–C(3)	1.513(3)	N(1)–C(6)–C(5)	118.0(2)
C(5)–C(20)	1.551(3)	O(6)–C(6)–C(5)	119.7(2)
O(13)–C(13)	1.214(3)	C(20)–C(5)–C(5)[a]	108.1(2)
C5–C5A[a]	1.574(4)		

[a]Symmetry transformation used to generate equivalent atoms: $-x+1, -y, -z+2$.

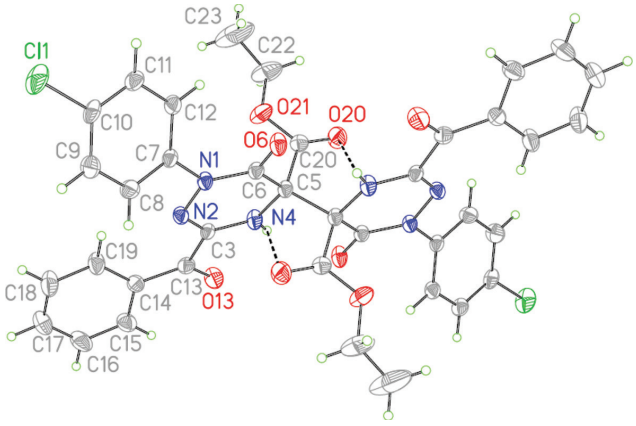


Fig. 2: ORTEP view of the molecular structure of **3a** in the crystal and atom numbering scheme adopted. Only one of the two crystallographically independent molecules is shown. Displacement ellipsoids are drawn at the 30% probability level, and hydrogen atoms are shown as spheres with arbitrary radii. The unlabeled atoms are generated by a center of inversion. N–H···O hydrogen bonding interactions are shown as dashed lines.

length is 1.574(4) Å and the corresponding bond length in the other crystallographically independent molecule is 1.579(19) Å, which is slightly longer than the average C–C single bond by 0.03 Å. The 1,3,4-thiadiazine ring is planar; the mean deviation of the atoms from average plane are 0.036 and 0.066 Å in the two half-molecules in the asymmetric unit. In each molecule, the two halves are linked by two N–H···O hydrogen bonding interactions as is shown in Fig. 2. The hydrogen bonding parameters are 2.16 Å, 2.716(3) Å, and 122.5° for H4···O6, N4···O6, and N4–H4···O6A, respectively. The corresponding distances and angles in the other molecule are 2.02 Å, 2.661(3) Å, and 130.8°.

The supramolecular structure is mainly developed based on chlorine···chlorine contacts and the nonclassical –H···O hydrogen bonding interaction. There are several weak hydrogen bonding interactions; these interactions will be ignored because of the abundance of C–H groups. Chlorine···chlorine contacts connect the molecular units to form a chain structure (Fig. 3), whereby the interchlorine distances are 3.351 and 3.336 Å; these distances are 0.15 and 0.17 Å less than the sum of the van der Waals radii. The C–Cl···Cl angles are 148.0° and 151.8°; these values are within the preferred values for these contacts [24]. Two types of chlorine···chlorine contacts are known: the symmetrical arrangement (also known as type I) and the perpendicular arrangement (known as type II). The observed chlorine···chlorine contacts, shown in Fig. 3, follow type I geometry [24].

3 Conclusion

A variety of substituted tetrahydro-5,5′-bi(1,2,4-triazin-6-ones) is prepared via the reaction of aminomalonic ester with various *N*-(aryl)hydrazonoyl chlorides in the presence of triethylamine. This versatile and efficient one-pot synthetic route uses readily available inexpensive

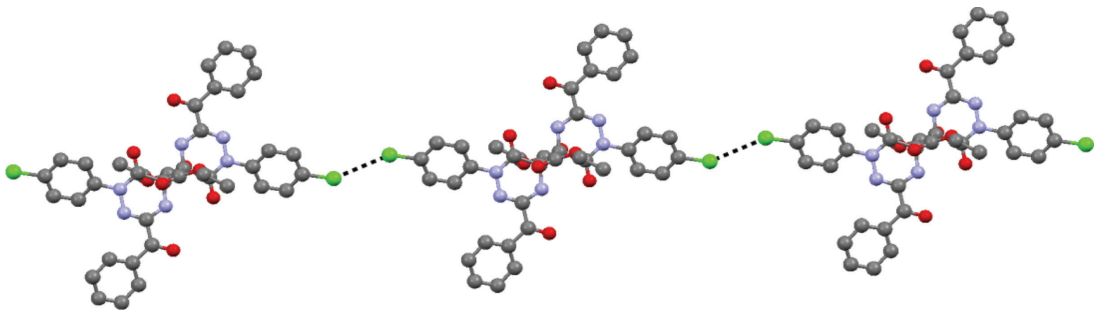


Fig. 3: Illustration of Cl···Cl contacts in **3a**.

reactants, is conveniently conducted at or below room temperature, and provides direct access to the desired dimmers decorated with a wide variety of substituents appended at *N*-1 and C-3 hetero-ring positions. The studies on biological activity of the synthesized compounds are currently underway.

4 Experimental section

Diethyl aminomalonate hydrochloride, 3-chloro-2,4-pentanedione, ethyl 3-chloroacetoacetate, 2-chloroacetophenone, methyl 4-aminobenzoate, aniline, and 4-(substituted)anilines were purchased from Acros (Geel, Belgium). Melting points (uncorrected) were determined on a Gallenkamp electrothermal melting temperature apparatus (London, UK) in open capillary tubes. IR spectra were recorded as KBr discs on a Nicolet Impact-400FT-IR spectrophotometer (Waltham, MA, USA). ^{1}H and ^{13}C NMR spectra were recorded on a 500-MHz Bruker Avance-III spectrometer (Bruker Daltonic, Bremen, Germany) with TMS as internal standard. Chemical shifts are expressed in δ units in ppm; J values for ^{1}H–^{1}H coupling constants are given in Hertz. HRMS data were acquired using the electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker APEX-IV (7 T) instrument (Karlsruhe, Germany).

4.1 *N*-(aryl)hydrazonoyl chlorides (I–III)

Compounds **Ic–g** [11, 25–27] and **IIa–f** [27–32] were reported in the literature and are prepared in this study via the Japp Klingemann reaction [33–36], which involves coupling of the appropriate arenediazonium chloride with the respective 3-chloro-2,4-pentanedione (or ethyl 2-chloroacetoacetate) following standard procedures [11]. Compounds **IIIa–e** [11, 27, 30, 37, 38] were prepared by coupling of the appropriate arenediazonium chloride with phenacyl chloride following reported procedures [11, 38].

4.2 General procedure for the synthesis of diethyl-1,1′-diaryl-5,5′-bis(dihydro-6-oxo-1,2,4-triazine)-5,5′-dicarboxylates (1–3)

A solution of diethyl aminomalonate hydrochloride (2.54 g, 0.012 mol) in ethanol (20 mL) was added to a solution of the appropriate hydrazonoyl chlorides **I–III** (0.01 mol) in ethanol (40 mL). Triethylamine (5 g, 0.05 mol) in ethanol (10 mL) was added to this resulting mixture, cooled in an ice-salt bath (T = 0–5°C). Thereafter, stirring was continued at T = ~0–5°C for 2 h and then at room temperature for 12 h. The reaction mixture was then diluted with cold H_2O (100 mL). The resulting solid product was collected by suction filtration, washed with cold water (2×20 mL), dried, and recrystallized from the appropriate solvent.

4.2.1 Diethyl 3,3′-diacetyl-6,6′-dioxo-1,1′-diphenyl-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylate (1c)

Yield: 77%; m. p. 141–142°C. – IR (KBr): ν_{max} = 3325, 1751, 1704, 1661 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 6H, 2CH_3CH$_2$O), 2.47 (s, 6H, 2CH$_3$C=O), 4.29 (q, J = 7.1 Hz, 4H, 2OCH_2Me), 7.39 (t, J = 7.6 Hz, 2H, 4″-H/4‴-H), 7.50 (overlapped dd, J = 7.6 Hz, 8.2 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.62 (d, J = 8.2 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.40 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (2 *C*H$_3$CH$_2$O), 23.8 (2*C*H$_3$C=O), 63.5 (2 OCH$_2$Me), 65.1 (C-5/C-5′), 125.3 (C-2″, C-6″/C-2‴, C-6‴), 127.8 (C-4″/C-4‴), 128.8 (C-3″, C-5″/C-3‴, C-5‴), 139.0 (C-3/C-3′), 140.5 (C-1″/C-1‴), 158.2 (C-6/C-6′), 166.9 (2 *C*O$_2$Et), 191.7 (2 Me-*C*=O) ppm. – HRMS ((+)-ESI): m/z = 577.20308 (calcd. 577.20414 for $C_{28}H_{29}N_6O_8$, $[M+H]^+$), 599.18575 (calcd. 599.18608 for $C_{28}H_{28}N_6O_8Na$, $[M+Na]^+$).

4.2.2 Diethyl 3,3′-diacetyl-1,1′-bis[4-(methoxycarbonyl)phenyl]-6,6′-dioxo-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylate (1d)

Yield: 88%; m. p. 178–179°C. – IR (KBr): ν_{max} = 3313, 1730, 1698, 1675, 1643, 860 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.0 Hz, 6H, 2 CH_3CH$_2$O), 2.51 (s, 6H, 2 CH$_3$C=O), 3.97 (s, 3H, CO$_2$CH_3), 4.29 (q, J = 7.0 Hz, 4H, 2 OCH_2Me), 7.75 (d, J = 8.6 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.16 (d, J = 8.6 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 8.39 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (2 *C*H$_3$CH$_2$O), 23.8 (2 *C*H$_3$C=O), 63.7 (2 OCH$_2$Me), 65.2 (C-5/C-5′), 124.6 (C-2″, C-6″/C-2‴, C-6‴), 129.3 (C-4″/C-4‴), 130.2 (C-3″, C-5″/C-3‴, C-5‴), 139.2 (C-3/C-3′), 144.1 (C-1″/C-1‴), 158.2 (C-6/C-6′), 166.3 (2 *C*O$_2$Me), 166.7 (2 *C*O$_2$Et), 191.5 (2 Me-*C*=O) ppm. – HRMS ((+)-ESI): m/z = 693.21565 (calcd. 693.21510 for $C_{32}H_{33}N_6O_{12}$, $[M+H]^+$).

4.2.3 Diethyl 3,3′-diacetyl-6,6′-dioxo-1,1′-di(4-methylphenyl)-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylate (1e)

Yield: 86%; m. p. 150–151°C. – IR (KBr): ν_{max} = 3325, 1746, 1702, 1662, 825 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.1 Hz, 6H, 2CH_3CH$_2$O), 2.38 (s, 6H, 4″-CH$_3$/4‴-CH$_3$), 2.42 (s, 6H, 2CH$_3$C=O), 4.24 (q, J = 7.1 Hz, 4H, 2OCH_2Me), 7.26 (d, J = 8.3 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 7.43 (d, J = 8.3 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 8.35 (br s, 2H, N(4)-H, N(4′)-H, exchangeable with D$_2$O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (2 CH$_3$CH$_2$O), 21.2 (4″-CH$_3$/4‴-CH$_3$), 23.8 (2CH$_3$C=O), 63.4 (2 OCH$_2$Me), 65.1 (C-5/C-5′), 125.1 (C-2″, C-6″/C-2‴, C-6‴), 129.5 (C-3″, C-5″/C-3‴, C-5‴), 137.9 (C-4″/C-4‴), 138.1 (C-1″/C-1‴), 139.0 (C-3/C-3′), 158.2 (C-6/C-6′), 167.0 (2 CO$_2$Et), 191.7 (2 Me-C=O) ppm. – HRMS ((+)-ESI): m/z = 605.23567 (calcd. 605.23544 for $C_{30}H_{33}N_6O_8$, $[M+H]^+$), 627.21647 (calcd. 627.21738 for $C_{30}H_{32}N_6O_8Na$, $[M+Na]^+$).

4.2.4 Diethyl 3,3′-diacetyl-1,1′-bis(4-cyanophenyl)-6,6′-dioxo-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylate (1f)

Yield: 78%; m. p. 178–179°C. – IR (KBr): ν_{max} = 3319, 2227, 1706, 1669, 839 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 6H, 2 CH_3CH$_2$O), 2.52 (s, 6H, 2 CH$_3$C=O), 4.28 (q, J = 7.0 Hz, 4H, 2 OCH_2Me), 7.78 (d, J = 8.5 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.83 (d, J = 8.5 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.35 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D$_2$O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (2 CH$_3$CH$_2$O), 23.8 (2 CH$_3$C=O), 63.9 (2 OCH$_2$Me), 65.2 (C-5/C-5′), 110.9 (C-4″/C-4‴), 118.0 (2 CN), 125.2 (C-2″, C-6″/C-2‴, C-6‴), 132.7 (C-3″, C-5″/C-3‴, C-5‴), 139.3 (C-3/C-3′), 143.8 (C-1″/C-1‴), 158.3 (C-6/C-6′), 166.5 (2 CO$_2$Et), 191.3 (2 Me-C=O) ppm. – HRMS ((+)-ESI): m/z = 627.19490 (calcd. 627.19464 for $C_{30}H_{27}N_8O_8$, $[M+H]^+$).

4.2.5 Diethyl 3,3′-diacetyl-1,1′-bis(4-methoxyphenyl)-6,6′-dioxo-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylate (1g)

Yield: 74%; m. p. 119–120°C. – IR (KBr): ν_{max} = 3329, 1744, 1701, 1661, 835 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 6H, 2CH_3CH$_2$O), 2.46 (s, 6H, 2CH$_3$C=O), 3.87 (s, 6H, 4″-OCH$_3$/4‴-OCH$_3$), 4.28 (q, J = 7.1 Hz, 4H, 2OCH_2Me), 7.01 (d, J = 8.8 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.50 (d, J = 8.8 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.39 (br s, 2H, N(4) H/N(4′)-H, exchangeable with D$_2$O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (2 CH$_3$CH$_2$O), 23.8 (2 CH$_3$C=O), 55.6 (4″-OCH$_3$/4‴-OCH$_3$), 63.4 (2 OCH$_2$Me), 65.0 (C-5/C-5′), 114.1 (C-3″, C-5″/C-3‴, C-5‴), 126.6 (C-2″, C-6″/C-2‴, C-6‴), 133.5 (C-1″/C-1‴), 139.0 (C-3/C-3′), 158.2 (C-4″/C-4‴), 159.0 (C-6/C-6′), 167.0 (2 CO$_2$Et), 191.7 (2 Me-C=O) ppm. – HRMS ((+)-ESI): m/z = 637.22504 (calcd. 637.22527 for $C_{30}H_{33}N_6O_{10}$, $[M+H]^+$), 659.20773 (calcd. 659.20721 for $C_{30}H_{32}N_6O_{10}Na$, $[M+Na]^+$).

4.2.6 Tetraethyl 1,1′-bis(4-chlorophenyl)-6,6′-dioxo-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-3,3′,5,5′-tetracarboxylate (2a)

Yield: 82%; m. p. 213–215°C. – IR (KBr): ν_{max} = 3333, 1746, 1726, 1668, 833 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 6H, CH_3CH$_2$CO$_2$-C3/CH_3CH$_2$CO$_2$-C3′), 1.38 (t, J = 7.1 Hz, 6H, CH_3CH$_2$CO$_2$-C5/CH_3CH$_2$CO$_2$-C5′), 4.32 (q, J = 7.1 Hz, 4H, CH$_3$CH_2CO$_2$-C5/CH$_3$CH_2CO$_2$-C5′), 4.39 (q, J = 7.1 Hz, 4H, CH$_3$CH_2CO$_2$-C3/CH$_3$CH_2CO$_2$-C3′), 7.43 (d, J = 8.6 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.54 (d, J = 8.6 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.56 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D$_2$O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (CH$_3$CH$_2$CO$_2$-C3/CH$_3$CH$_2$CO$_2$-C3′), 14.1 (CH$_3$CH$_2$CO$_2$-C5/CH$_3$CH$_2$CO$_2$-C5′), 63.4 (CH$_3$$CH_2CO_2$-C3/CH$_3$$CH_2CO_2$-C3′), 63.8 (CH$_3CH_2CO_2$-C5/CH$_3CH_2CO_2$-C5′), 65.1 (C-5/C-5′), 126.8 (C-2″, C-6″/C-2‴, C-6‴), 129.0 (C-3″, C-5″/C-3‴, C-5‴), 133.5 (C-4″/C-4‴), 134.7 (C-1″/C-1‴) 138.8 (C-3/C-3′), 157.9 (C-6/C-6′), 159.7 (C3-CO$_2$Et/C3′-CO$_2$Et), 166.6 (C5-CO$_2$Et/C5′-CO$_2$Et) ppm. – HRMS ((+)-ES1): m/z = 705.14740, (calcd. 705.14732 for $C_{30}H_{31}{}^{35}Cl_2N_6O_{10}$, $[M+H]^+$), 707.14492 (calcd. 707.14533 for $C_{30}H_{31}{}^{35}Cl^{37}Cl\ N_6O_{10}$, $[M+2+H]^+$), 709.14081 (calcd. 709.14143 for $C_{30}H_{31}{}^{37}Cl_2N_6O_{10}$, $[M+4+H]^+$).

4.2.7 Tetraethyl 1,1′-bis(4-bromophenyl)-6,6′-dioxo-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-3,3′,5,5′-tetracarboxylate (2b)

Yield: 75%; m. p. 230–233°C. – IR (KBr): ν_{max} = 3332, 1746, 1724, 1668, 830 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 6H, CH_3CH$_2$CO$_2$-C3/CH_3CH$_2$CO$_2$-C3′), 1.39 (t, J = 7.1 Hz, 6H, CH_3CH$_2$CO$_2$-C5/CH_3CH$_2$CO$_2$-C5′), 4.31 (q, J = 7.1 Hz, 4H, CH$_3$CH_2CO$_2$-C5/CH$_3$CH_2CO$_2$-C5′), 4.40 (q, J = 7.1 Hz, 4H, CH$_3$CH_2CO$_2$-C3/CH_3CH$_2$CO$_2$-C3′), 7.48 (d, J = 8.6 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.58 (d, J = 8.6 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.55 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D$_2$O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (CH$_3$CH$_2$CO$_2$-C3/CH$_3$CH$_2$CO$_2$-C3′), 14.1 (CH$_3$CH$_2$CO$_2$-C5/CH$_3$CH$_2$CO$_2$-C5′), 63.4 (CH$_3$$CH_2CO_2$-C3/CH$_3$$CH_2CO_2$-C3′), 63.8 (CH$_3CH_2CO_2$-C5/CH$_3CH_2CO_2$-C5′), 65.1 (C-5/C-5′), 121.5 (C-4″/C-4‴), 127.1 (C-2″, C-6″/C-2‴, C-6‴), 132.0 (C-3″,

C-5″/C-3‴, C-5‴), 134.7 (C-1″/C-1‴) 139.3 (C-3/C-3′), 157.9 (C-6/C-6′), 159.6 (C3-*C*O$_2$Et/C3′-*C*O$_2$Et), 166.6 (C5-*C*O$_2$Et/C5′-*C*O$_2$Et) ppm. – HRMS (ES1): *m/z* = 793.04580 (calcd. 793.04629 for $C_{30}H_{31}{}^{79}Br_2N_6O_{10}$, $[M+H]^+$), 795.04570 (calcd. 795.04455 for $C_{30}H_{31}{}^{79}Br^{81}BrN_6O_{10}$, $[M+2+H]^+$), 797.04340 (calcd. 797.04331 for $C_{30}H_{31}{}^{81}Br_2N_6O_{10}$, $[M+4+H]^+$), 815.02823 (calcd. 815.02824 for $C_{30}H_{30}{}^{79}Br_2N_6O_{10}$ Na, $[M+Na]^+$), 817.02593 (calcd. 817.02650 for $C_{30}H_{30}N_6O_{10}{}^{79}Br^{81}BrNa$, $[M+2+Na]^+$), 819.02583 (calcd. 819.02526 for $C_{30}H_{30}{}^{81}Br_2N_6O_{10}Na$, $[M+4+Na]^+$).

4.2.8 Tetraethyl 6,6′-dioxo-1,1′-diphenyl-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-3,3′,5,5′-tetracarboxylate (2c)

Yield: 87%; m. p. 218–223°C. – IR (KBr): ν_{max} = 3328, 1743, 1719, 1666 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$CO$_2$-C3/C*H*$_3$CH$_2$CO$_2$-C3′), 1.37 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$CO$_2$-C5/C*H*$_3$CH$_2$CO$_2$-C5′), 4.34 (q, *J* = 7.1 Hz, 4H, CH$_3$C*H*$_2$CO$_2$-C5/CH$_3$C*H*$_2$CO$_2$-C5′), 4.39 (q, *J* = 7.1 Hz, 4H, CH$_3$C*H*$_2$CO$_2$-C3/CH$_3$C*H*$_2$CO$_2$-C3′), 7.37 (t, *J* = 7.3 Hz, 2H, 4″-H, 4‴-H), 7.47 (pseudo t, *J* = 7.7 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.58 (d, *J* = 7.7 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.60 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (*C*H$_3$CH$_2$CO$_2$-C3/*C*H$_3$CH$_2$CO$_2$-C3′), 14.1 (*C*H$_3$CH$_2$CO$_2$-C5/*C*H$_3$CH$_2$CO$_2$-C5′), 63.3 (CH$_3$*C*H$_2$CO$_2$-C3/CH$_3$*C*H$_2$CO$_2$-C3′), 63.6 (CH$_3$*C*H$_2$CO$_2$-C5/CH$_3$*C*H$_2$CO$_2$-C5′), 65.1 (C-5/C-5′), 125.7 (C-2″, C-6″/C-2‴, C-6‴), 128.0 (C-4″/C-4‴), 128.9 (C-3″, C-5″/C-3‴, C-5‴), 134.6 (C-1″/C-1‴), 140.4 (C-3/C-3′), 157.9 (C-6/C-6′), 159.8 (C3-*C*O$_2$Et/C3′-*C*O$_2$Et), 166.8 (C5-*C*O$_2$Et/C5′-*C*O$_2$Et) ppm. – HRMS ((+)-ESI): *m/z* = 637.22572 (calcd. 637.22527 for $C_{30}H_{33}N_6O_{10}$, $[M+H]^+$).

4.2.9 Tetraethyl 1,1′-bis[4-(methoxycarbonyl)phenyl]-6,6′-dioxo-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-3,3′,5,5′-tetracarboxylate (2d)

Yield: 91%; m. p. 198–200°C. – IR (KBr): ν_{max} = 3310, 1725, 1673, 1651, 860 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$CO$_2$-C3/C*H*$_3$CH$_2$CO$_2$-C3′), 1.38 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$CO$_2$-C5/C*H*$_3$CH$_2$CO$_2$-C5′), 3.95 (s, 6H, C4″-CO$_2$C*H*$_3$/C4‴-CO$_2$C*H*$_3$), 4.32 (q, *J* = 7.1 Hz, 4H, CH$_3$C*H*$_2$CO$_2$-C5/CH$_3$C*H*$_2$CO$_2$-C5′), 4.39 (q, *J* = 7.1 Hz, 4H, CH$_3$C*H*$_2$CO$_2$-C3/CH$_3$C*H*$_2$CO$_2$-C3′), 7.71 (d, *J* = 8.6 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 8.13 (d, *J* = 8.6 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.57 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (*C*H$_3$CH$_2$CO$_2$-C3/*C*H$_3$CH$_2$CO$_2$-C3′), 14.0 (2 *C*H$_3$CH$_2$CO$_2$-C5/*C*H$_3$CH$_2$CO$_2$-C5′), 52.3 (C4″-CO$_2$*C*H$_3$/C4‴-CO$_2$*C*H$_3$), 63.5 (CH$_3$*C*H$_2$CO$_2$-C3/CH$_3$*C*H$_2$CO$_2$-C3′), 63.9 (CH$_3$*C*H$_2$CO$_2$-C5/CH$_3$*C*H$_2$CO$_2$-C5′), 65.2 (C-5/C-5′), 125.0 (C-2″, C-6″/C-2‴, C-6‴), 129.1 (C-4″/C-4‴), 130.3 (C-3″, C-5″/C-3‴, C-5‴), 134.8 (C-3/C-3′), 144.0 (C-1″/C-1‴), 158.0 (C-6/C-6′), 159.7 (C3-*C*O$_2$Et/C3′-*C*O$_2$Et), 166.4 (C4″-*C*O$_2$CH$_3$/C4‴-*C*O$_2$CH$_3$) 166.5 (C5-*C*O$_2$Et/C5′-*C*O$_2$Et) ppm. – HRMS ((+)-ESI): *m/z* = 775.21782 (calcd. 775.21817 for $C_{34}H_{36}N_6O_{14}Na$, $[M+Na]^+$), 1527.44658 (calcd. 1527.44712 for $C_{68}H_{72}N_{12}O_{28}Na$, $[2M+Na]^+$).

4.2.10 Tetraethyl 6,6′-dioxo-1,1′-di(4-methylphenyl)-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-3,3′,5,5′-tetracarboxylate (2e)

Yield: 76%; m. p. 218–220°C. – IR (KBr): ν_{max} = 3294, 1743, 1722, 1665, 861 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$CO$_2$-C3/C*H*$_3$CH$_2$CO$_2$-C3′), 1.36 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$CO$_2$-C5/C*H*$_3$CH$_2$CO$_2$-C5′), 2.40 (s, 6H, 4″-C*H*$_3$/4‴-C*H*$_3$) 4.33 (q, *J* = 7.1 Hz, 4H, CH$_3$C*H*$_2$CO$_2$-C5/CH$_3$C*H*$_2$CO$_2$-C5′), 4.38 (q, *J* = 7.1 Hz, 4H, CH$_3$C*H*$_2$CO$_2$-C3/C*H*$_3$C*H*$_2$CO$_2$-C3′), 7.27 (d, *J* = 8.2 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.44 (d, *J* = 8.2 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.59 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (*C*H$_3$CH$_2$CO$_2$-C3/*C*H$_3$CH$_2$CO$_2$-C3′), 14.1 (*C*H$_3$CH$_2$CO$_2$-C5/*C*H$_3$CH$_2$CO$_2$-C5′), 21.2 (4″-CH$_3$/4‴-CH$_3$), 63.2 (CH$_3$*C*H$_2$CO$_2$-C3/CH$_3$*C*H$_2$CO$_2$-C3′), 63.5 (CH$_3$*C*H$_2$CO$_2$-C5/CH$_3$*C*H$_2$CO$_2$-C5′), 65.1 (C-5/C-5′), 125.5 (C-3″, C-5″/C-3‴, C-5‴), 129.5 (C-2″, C-6″/C-2‴, C-6‴), 134.5 (C-1″/C-1‴), 137.9 (C-4″/C-4‴), 137.9 (C-3/C-3′), 157.9 (C-6/C-6′), 159.8 (C3-*C*O$_2$Et/C3′-*C*O$_2$Et), 166.8 (C5-*C*O$_2$Et/C5′-*C*O$_2$Et) ppm. – HRMS ((+)-ES1): *m/z* = 665.25608, (calcd. 665.25657 for $C_{32}H_{37}N_6O_{10}$, $[M+H]^+$).

4.2.11 Tetraethyl 1,1′-bis(4-cyanophenyl)-6,6′-dioxo-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-3,3′,5,5′-tetracarboxylate (2f)

Yield: 92%; m. p. 220–222°C. – IR (KBr): ν_{max} = 3301, 2232, 1744, 1677, 851 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$CO$_2$-C3/C*H*$_3$CH$_2$CO$_2$-C3′), 1.38 (t, *J* = 7.1 Hz, 6H, C*H*$_3$CH$_2$CO$_2$-C5/C*H*$_3$CH$_2$CO$_2$-C5′), 4.30 (q, *J* = 7.1 Hz, 4H, CH$_3$C*H*$_2$CO$_2$-C5/CH$_3$C*H*$_2$CO$_2$-C5′), 4.40 (q, *J* = 7.1 Hz, 4H, CH$_3$C*H*$_2$CO$_2$-C3/C*H*$_3$C*H*$_2$CO$_2$-C3′), 7. 74 (d, *J* = 8.6 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.79 (d, *J* = 8.6 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.54 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (*C*H$_3$CH$_2$CO$_2$-C3/*C*H$_3$CH$_2$CO$_2$-C3′), 14.0 (2 *C*H$_3$CH$_2$CO$_2$-C5/*C*H$_3$CH$_2$CO$_2$-C5′), 63.6 (CH$_3$*C*H$_2$CO$_2$-C3/CH$_3$*C*H$_2$CO$_2$-C3′), 64.0 (CH$_3$*C*H$_2$CO$_2$-C5/CH$_3$*C*H$_2$CO$_2$-C5′), 65.2 (C-5/C-5′), 111.1 (C-4″/C-4‴), 118.3 (2 CN), 125.5 (C-2″,

C-6″/C-2‴, C-6‴), 132.8 (C-3″, C-5″/C-3‴, C-5‴), 135.0 (C-1″/C-1‴) 143.8 (C-3/C-3′), 158.0 (C-6/C-6′), 159.5 (C3-*C*O$_2$Et/C3′-*C*O$_2$Et), 166.4 (C5-*C*O$_2$Et/C5′-*C*O$_2$Et) ppm. – HRMS ((+)-ESI): *m/z* = 687.21632 (calcd. 687.21577 for $C_{32}H_{31}N_8O_{10}$, $[M+H]^+$).

4.2.12 Diethyl 3,3′-dibenzoyl-1,1′-bis(4-chlorophenyl)-6,6′-dioxo-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylate (3a)

Yield: 83%; m. p. 212–214°C. – IR (KBr): ν_{max} = 3311, 1746, 1670, 1655, 833 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, 6H, 2 C*H*$_3$CH$_2$O), 4.32 (q, 4H, 2 OC*H*$_2$Me), 7.45 (d, *J* = 8.9 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.46 (pseudo t, 4H, *J* = 7.5, 3‴-H, 5‴-H/3⁗-H, 5⁗-H), 7.60 (d, *J* = 8.9 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 7.62 (dd, 2H, *J* = 7.5, 2.0, H-4⁗/H-4⁗), 8.24 (d, 4H, *J* = 7.5, 2⁗-H, 6⁗-H/2⁗-H, 6⁗-H), 8.67 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.0 (2 *C*H$_3$CH$_2$O), 63.7 (2 OCH$_2$Me), 65.5 (C-5/C-5′), 126.8 (C-2″, C-6″/C-2‴, C-6‴), 128.1 (C-3⁗, C-5⁗/C-3⁗, C-5⁗), 128.9 (C-3″, C-5″/C-3‴, C-5‴), 131.1 (C-2⁗, C-6⁗/C-2⁗, C-6⁗) 133.1 (C-4″/C-4‴), 133.6 (C-4⁗/C-4⁗) 134.4 (C-1″/C-1‴), 139.0 (C-3/C-3′), 139.6 (C-1⁗/C-1⁗) 158.0 (C-6/C-6′), 166.8 (2 *C*O$_2$Et), 184.4 (2 Ph-*C*=O) ppm. – HRMS ((–)-ESI): *m/z* = 767.14276 (calcd. 767.14294 for $C_{38}H_{29}{}^{35}Cl_2N_6O_8$, $[M-H]^-$), 769.14183 (calcd. 769.14129 for $C_{38}H_{29}{}^{35}Cl^{37}ClN_6O_8$, $[M+2-H]^-$), 771.13528(calcd. 771.13595 for $C_{38}H_{29}{}^{37}Cl_2N_6O_8$, $[M+4-H]^-$).

Yellow needle-like crystals of **3a**, suitable for X-ray crystallography, were grown slowly by allowing a clear dilute solution of **3a** in ethanol to stand in an open vessel at room temperature for 10–12 days.

4.2.13 Diethyl 3,3′-dibenzoyl-1,1′-bis(4-bromophenyl)-6,6′-dioxo-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylate (3b)

Yield: 85%; m. p. 208–210°C. – IR (KBr): ν_{max} = 3306, 1743, 1669, 1665, 828 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.0 Hz, 6H, 2 C*H*$_3$CH$_2$O), 4.32 (q, *J* = 7.0 Hz, 4H, 2 OC*H*$_2$Me), 7.46 (pseudo t, *J* = 7.8 Hz, 4H, 3⁗-H, 5⁗-H/3⁗-H, 5⁗-H), 7.55 (d, *J* = 8.7 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 7.60 (t, H-4⁗/H-4⁗), 7.61 (d, *J* = 8.7 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 8.23 (d, *J* = 7.5 Hz, 4H, 2⁗-H, 6⁗-H/2⁗-H, 6⁗-H), 8.66 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (2 *C*H$_3$CH$_2$O) 63.7 (2 OCH$_2$Me), 65.4 (C-5/C-5′), 121.1 (C-4″/C-4‴), 126.6 (C-2″, C-6″/C-2‴, C-6‴), 128.2 (C-3⁗, C-5⁗/C-3⁗, C-5⁗), 131.1 (C-2⁗, C-6⁗/C-2⁗, C-6⁗), 131.9 (C-3″, C-5″/C-3‴, C-5‴), 133.6 (C-4⁗/C-4⁗), 134.4 (C-1⁗/C-1⁗), 139.5 (C-1″/C-1‴), 139.7 (C-3/C-3′), 157.9 (C-6/C-6′), 166.8 (2 *C*O$_2$Et), 184.4 (2 Ph-*C*=O) ppm. – HRMS ((–)-ESI): *m/z* = 855.04226 (calcd. 855.04191 for $C_{38}H_{29}{}^{79}Br_2N_6O_8$, $[M-H]^-$), 857.04104 (calcd. 857.04029 for $C_{38}H_{29}{}^{79}Br^{81}BrN_6O_8$, $[M+2-H]^-$), 859.04021 (calcd. 859.03932 for $C_{38}H_{29}{}^{81}Br_2N_6O_8$, $[M+4-H]^-$).

4.2.14 Diethyl 3,3′-dibenzoyl-6,6′-dioxo-1,1′-diphenyl-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylate (3c)

Yield: 82%; m. p. 205–207°C. – IR (KBr): ν_{max} = 3308, 1747, 1670, 1656 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 6H, 2 C*H*$_3$CH$_2$O), 4.28 (q, *J* = 7.0 Hz, 4H, 2 OC*H*$_2$Me), 7.34 (t, *J* = 7.5 Hz, 2H, H-4″/H-4‴), 7.42 (pseudo t, *J* = 7.8 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.46 (pseudo t, *J* = 7.7 Hz, 4H 3⁗-H, 5⁗-H/3⁗-H, 5⁗-H), 7.56 (t, *J* = 7.5 Hz, H-4⁗/H-4⁗), 7.62 (d, *J* = 7.7 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.23 (d, *J* = 7.4 Hz, 4H, 2⁗-H, 6⁗-H/2⁗-H, 6⁗-H), 8.68 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2 (2 *C*H$_3$CH$_2$O), 63.7 (2 OCH$_2$Me), 65.7 (C-5/C-5′), 125.3 (C-2″, C-6″/C-2‴, C-6‴), 127.8 (C-4″/C-4‴), 128.3 (C-3⁗, C-5⁗/C-3⁗, C-5⁗) 129.0 (C-3″, C-5″/C-3‴, C-5‴), 131.4 (C-2⁗, C-6⁗/C-2⁗, C-6⁗), 133.7 (C-4⁗/C-4⁗), 134.8 (C-1″/C-1‴), 139.8 (C-3/C-3′), 140.8 (C-1⁗/C-1⁗), 158.2 (C-6/C-6′), 167.2 (2 *C*O$_2$Et), 184.7 (2 Ph-*C*=O) ppm. – HRMS (ESI): *m/z* = 701.23601 (calcd. 701.23544 for $C_{38}H_{33}N_6O_8$, $[M+H]^+$), 699.22168 (calcd. 699.22089 for $C_{38}H_{31}N_6O_8$, $[M-H]^-$).

4.2.15 Diethyl 3,3′-dibenzoyl-1,1′-bis[4-(methoxycarbonyl)phenyl]-6,6′-dioxo-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylate (3d)

Yield: 87%; m. p. 192–194°C. – IR (KBr): ν_{max} = 3310, 1742, 1718, 1655, 865 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, 6H, 2 C*H*$_3$CH$_2$O), 3.97 (s, 6H, 2CO$_2$-CH$_3$), 4.32 (q, 4H, 2 OC*H*$_2$Me), 7.47 (pseudo t, *J* = 7.8 Hz, 4H, 3⁗-H, 5⁗-H/3⁗-H, 5⁗-H), 7.62 (t, *J* = 7.5 Hz, 4H, H-4⁗/H-4⁗), 7.78 (d, *J* = 8.6 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 8.15 (d, *J* = 8.6 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 8.25 (d, *J* = 7.5 Hz, 4H, 2⁗-H, 6⁗-H/2⁗-H, 6⁗-H), 8.69 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (2 *C*H$_3$CH$_2$O), 52.3 (2CO$_2$-*C*H$_3$), 63.8 (2 OCH$_2$Me), 65.4 (C-5/C-5′), 124.4 (C-2″, C-6″/C-2‴, C-6‴), 128.2 (C-3⁗, C-5⁗/C-3⁗, C-5⁗), 128.8 (C-4″/C-4‴), 130.2 (C-3″, C-5″/C-3‴, C-5‴), 131.1 (C-2⁗, C-6⁗/C-2⁗, C-6⁗), 133.7 (C-4⁗/C-4⁗), 134.3 (C-1⁗/C-1⁗),

139.6 (C-3/C-3′), 144.2 (C-1″/C-1‴), 158.0 (C-6/C-6′), 166.4 (2 CO_2Me), 166.8 (2 CO_2Et), 184.4 (2 Ph-*C*=O) ppm. – HRMS ((−)-ESI): m/z = 815.23097 (calcd. 815.23184 for $C_{42}H_{35}N_6O_{12}$, $[M-H]^-$).

4.2.16 Diethyl 3,3′-dibenzoyl-6,6′-dioxo-1,1′-di(4-methylphenyl)-1,1′,4,4′,5,5′,6,6′-octahydro-5,5′-bi(1,2,4-triazine)-5,5′-dicarboxylate (3e)

Yield: 92%; m. p. 210–211°C. – IR (KBr): ν_{max} = 3299, 1739, 1668, 1645, 824 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, 6H, 2 CH_3CH$_2$O), 2.39 (s, 6H, Ar-CH3), 4.28 (q, 4H, 2 OCH_2Me), 7.26 (d, J = 8.9 Hz, 4H, 2″-H, 6″-H/2‴-H, 6‴-H), 7.41 (pseudo t, J = 7.8, 4H 3‴-H, 5⁗-H/3⁗-H, 5⁗-H), 7.50 (d, J = 8.0 Hz, 4H, 3″-H, 5″-H/3‴-H, 5‴-H), 7.55 (t, J = 7.4, H-4⁗/H-4⁗), 8.22 (d, J = 7.4 Hz, 4H, 2⁗-H, 6⁗-H/2⁗-H, 6⁗-H), 8.67 (br s, 2H, N(4)-H/N(4′)-H, exchangeable with D_2O) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (2 CH_3CH$_2$O), 21.2 (Ar-*C*H3), 63.5 (2 OCH$_2$Me), 65.4 (C-5/C-5′), 125.0 (C-2″, C-6″/C-2‴, C-6‴), 128.1 (C-3⁗, C-5⁗/C-3⁗, C-5⁗) 129.4 (C-3″, C-5″/C-3‴, C-5‴), 131.2 (C-2⁗, C-6⁗/C-2⁗, C-6⁗) 133.4 (C-4⁗/C-4⁗) 134.6 (C-1″/C-1‴), 138.2 (C-4″/C-4‴), 139.6 (C-1⁗/C-1⁗), 140.0 (C-3/C-3′), 158.0 (C-6/C-6′), 167.1 (2 CO_2Et), 184.5 (2 Ph-*C*=O) ppm. – HRMS ((+)-ESI): m/z = 751.24813 (calcd. 751.24868 for $C_{40}H_{36}N_6O_8Na$, $[M+Na]^+$), 1479.50786 (calcd. 1479.50815 for $C_{80}H_{72}N_{12}O_{16}Na$, $[2M+Na]^+$).

4.3 Collection of X-ray diffraction data and structure analysis of 3a

A suitable single crystal of **3a** (approximate dimensions of 0.31 × 0.19 × 0.09 mm^3) was epoxy-mounted on a glass fiber. Data were collected at room temperature (T = 293 K) using an Oxford Calibur diffractometer. Data were then acquired and processed to give SHELX-format *hkl* files using CRYSALISPRO software [39]. Cell parameters were determined and refined using CRYSALISPRO [39]. A multiscan absorption collection was applied with minimum and maximum transmission factors of 1.000 and 0.255, respectively. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using all unique data [40]. All nonhydrogen atoms were refined anisotropically with the hydrogen atoms placed in calculated positions and refined using a riding model.

CCDC 1815322 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

5 Supporting information

^{1}H and ^{13}C NMR spectra of representative compounds **1e** (Figs. S1–S5), **2e** (Figs. S6–S10), and **3e** (Figs. S11–S13) are given as supplementary material available online (DOI: 10.1515/znb-2018-0148).

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Graphical synopsis

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Bis-heterocycles. Part I: tetrahydro-5,5′-bi(1,2,4-triazin-6-ones)

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