Studies on Pyrrolidinones: Chemistry of Dimethoxytriazines

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Abstract: The synthesis of dimethoxytriazine-containing *N*-aryl substituted pyrrolidinones is realized for the first time. Three new modes of reactivity for these substrates possessing a 4,6-dimethoxy-1,3,5-triazine unit are discussed. Their treatment with acid leads to complete O-demethylation of the methoxy groups, while similar reaction in a basic medium leads to partial O-demethylation. In contrast, heating in the presence of dimethyl sulfate as the catalyst induces migration of the methyl groups from the oxygen atoms to the triazine nitrogens (Hilbert–Johnson transposition). These new scaffolds may demonstrate biological potential.

Key words: arylation, cleavage, carboxylic acids, zinc, ring closure

The *s*-triazine (1,3,5-triazine) moiety is a widespread heterocyclic system, which can be utilized as a synthetic pharmacophore with considerable therapeutic potential.[1] While less studied than pyrimidines, the biological importance of triazines has made them attractive synthetic targets. Many derivatives of this class of compounds have been synthesized, mainly for their antifungal[2] and herbicidal[3] properties. We have previously reported that several *N*-benzylpyrrolidinones, such as **1**[4] and **2**,[5] exhibit antifungal activities, and have investigated the synthesis of heterocyclic compounds **3** containing an *N*-benzylpyrrolidinone group linked to a 4,6-dimethoxy-1,3,5-triazine moiety, with potential biostatic properties[6] (Figure 1). In continuation of this research, we were interested by the possibility of attaching 1,3,5-triazinone and 1,3,5-triazinedione cores to pyrrolidinones (at C-5). Herein, we report the synthesis of novel triazines **3** and **4**, the total or partial hydrolysis of their methoxy groups, and the Hilbert–Johnson transposition of these compounds.

Important methods described thus far for the synthesis of dimethoxytriazines involve the Grignard or palladium-catalyzed coupling of 2-chloro-4,6-dimethoxytriazine,[7] or the reaction of a very large excess of an activated carboxylic acid with zinc dimethyl imidodicarbonimidate (**5**).[8] We previously reported that performing this reaction in the presence of pyridine and 4 Å molecular sieves allowed the use of only a stoichiometric amount of acid chloride, affording the known dimethoxytriazines **3a** and **3b**.[6] The same reaction applied to the condensation of acid chlorides **6c**,[9] **7a** and **7b** furnished moderate to good yields of

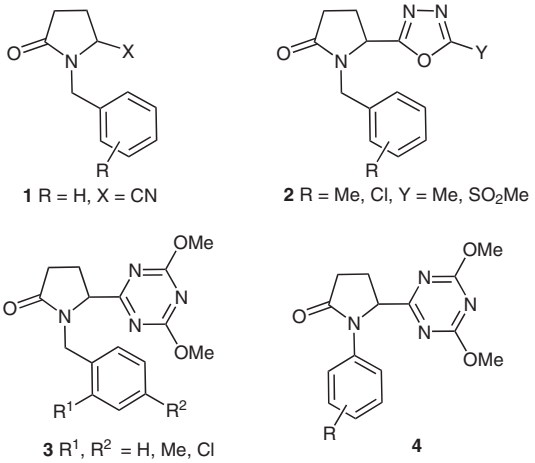

Figure 1 Structures of *N*-benzylpyrrolidinones **1**, **2** and **3**

the novel dimethoxytriazines **3c**, **4a** and **4b** (Scheme 1). Acid chlorides **7a** and **7b** were obtained via the copper-catalyzed N-arylation of methyl DL-pyroglutamate (**8**),[10,11] saponification of the intermediate esters **9a**[10] and **9b** thus obtained, and then treatment of the acids **10a** and **10b** with thionyl chloride (Scheme 1).

There are no reports on the synthesis of 2-alkyltriazine-4,6-diones in the literature. In the field of dialkoxytriazines substituted at C-2 by an amino[12] or a propargyloxy[13] group, reflux of the substrate in dilute hydrochloric acid or heating at 180 °C led to the formation of the corresponding di- (or tri)-carbonyl compound. In the dimethoxypyrimidine series, many different reagents have been utilized to realize such total hydrolysis (Me_3SiX[14] in the presence of NaI,[15] CH_3COX[16] which is considered to be better,[15b] or heating in aqueous HCl,[17] which is described[18] as the superior method). Nevertheless, with dimethoxypyridine[19] or pyrimidine,[20] partial hydrolysis can occur, sometimes accompanied by migration of one of the methyl groups from oxygen to nitrogen. We studied the hydrolysis of dimethoxytriazine **3a** in 20% aqueous hydrochloric acid (4 equiv, reflux, 3 h), which resulted in complete decomposition of the substrate. However, heating the same compound at reflux temperature in aqueous hydrochloric acid (1.8%) for five hours furnished a 71% yield of triazinedione **11a** after recrystallization from water. Thus, hydrolysis of compounds **3b**, **3c**, **4a** and **4b** was realized under these conditions to afford products **11b**, **11c**, **12a** and **12b** in moderate to good yields

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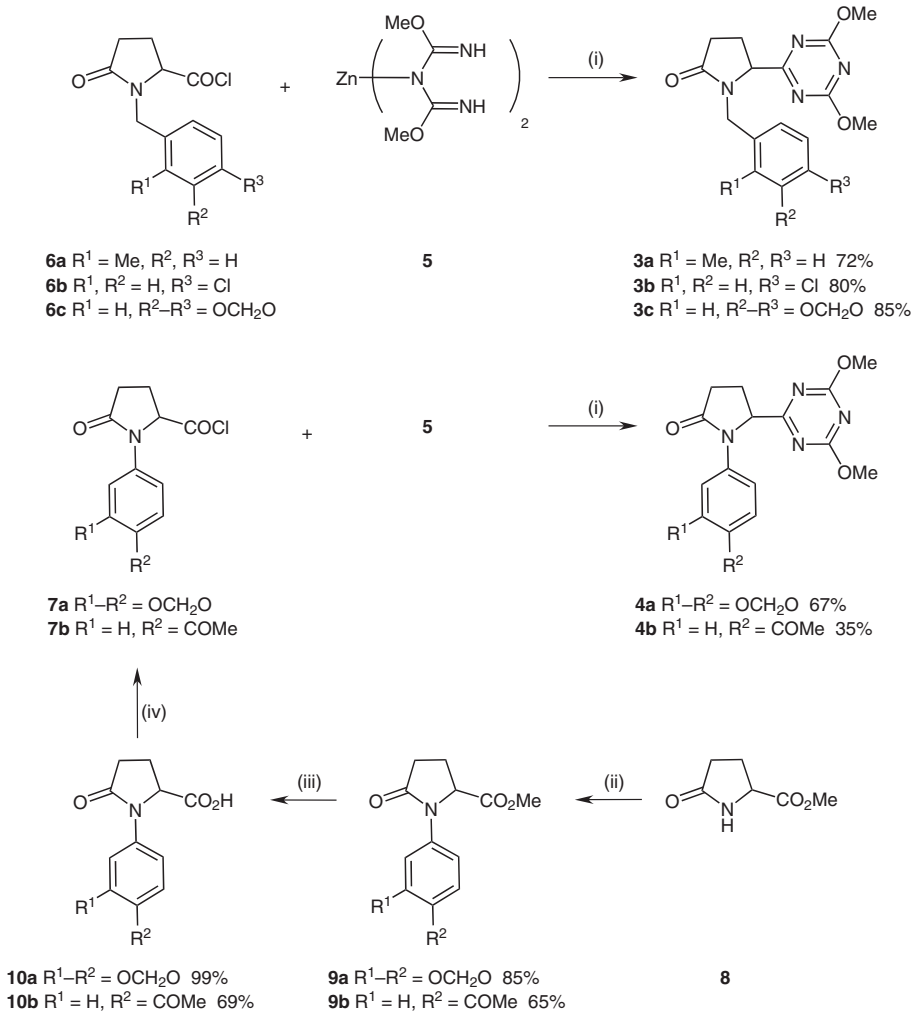
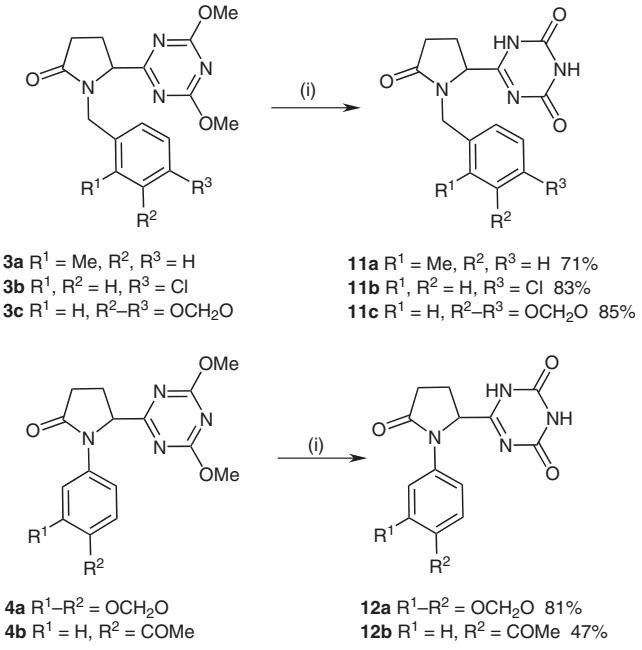


Scheme 1 *Reagents and conditions*: (i) py, powdered 4 Å MS, CH_2Cl_2, r.t., 24 h; (ii) aryl halide (1–1.5 equiv), CuI (0.5 equiv), *N*,*N*′-dimethylethylenediamine (1 equiv), Cs_2CO_3 (2 equiv), 1,4-dioxane, inert atm, 50–60 °C, 6–20 h; (iii) aq NaOH (2 M, 2 equiv), 80 °C, 1–10 h, then HCl; (iv) $SOCl_2$ (2 equiv), CH_2Cl_2, inert atm, reflux, 2–24 h, quant.

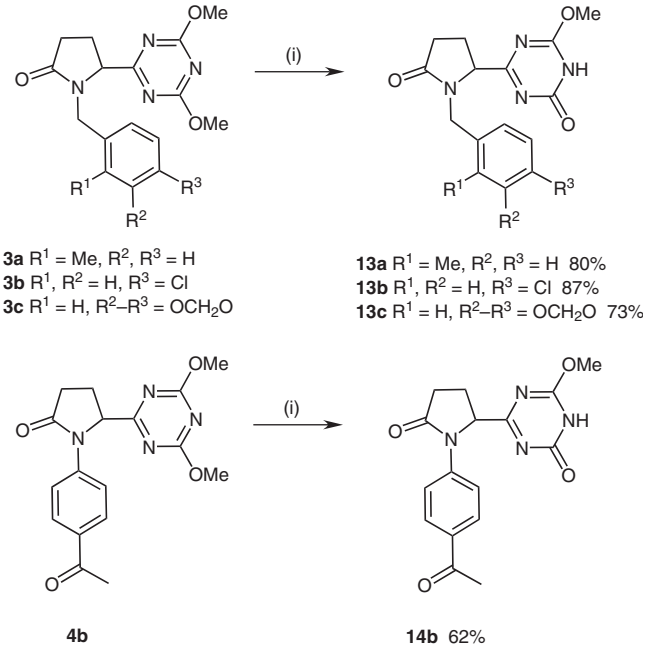
(Scheme 2). Interestingly, during these reactions with hydrochloric acid, partial hydrolysis or migration of a methyl group were not detected.

As with the total hydrolysis of alkoxytriazines, the literature proved to be very scarce concerning partial reactions. To the best of our knowledge, the only reports concerned heating 2,4,6-tripropargyloxy-1,3,5-triazines (50 °C, 1 h) in aqueous sodium hydroxide (5%), which led to hydrolysis of one of the three ether groups,[13b] and the analogous reaction in the 2,4-dimethoxy-1,3-pyrimidine series required heating the substrate at reflux temperature in aqueous sodium hydroxide (5 M) for 48 hours to give moderate yields of methoxypyrimidone, accompanied by the completely hydrolyzed product.[20] Modification of these conditions led us to heat dimethoxytriazines **3a**–**c** and **4b** at reflux temperature in the presence of potassium hydroxide (1–2 equiv) in methanol for 20–28 hours to give 62–87% yields of 2-methoxy-1,3,5-triazin-6-ones **13a**–**c** and **14b** (Scheme 3); no by-products were isolated from these reactions.

1,3-Dimethyl-1,3,5-triazine-2,4-diones represent other potential biocides; these interesting compounds can be obtained by Hilbert–Johnson oxygen to nitrogen migration of dimethoxytriazines. The mechanism of the reaction was proved, in the pyrimidine series, to occur via a sequence of alkylation–dealkylation steps,[21] at 160–190 °C in the presence of *p*-toluenesulfonic acid (PTSA) derivatives,[22] or at lower temperatures by using alkylating agents,[23] or sodium iodide in *N*,*N*-dimethylformamide.[24] Again, very few reports have appeared concerning the triazine series: 2,3-dimethoxy-1,3,5-triazine[25] and 1-amino-3,5-dialkoxytriazines,[22b] were transposed at high temperature (160–250 °C), the reaction being favored by the action of *p*-toluenesulfonic acid. In addition, the reaction of 2-chloro-3,5-dimethoxytriazine with sodium diethoxy dithiophosphonate led to the product of oxygen to nitrogen

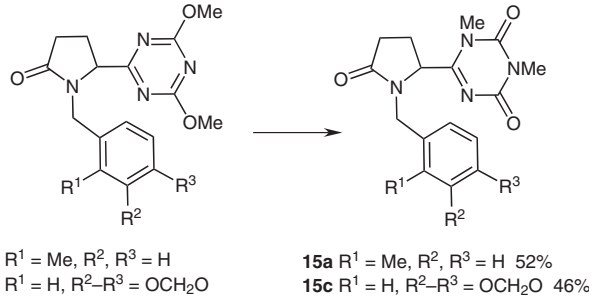


Scheme 2 *Reagents and conditions*: (i) aq HCl (1.8%, 2 equiv), reflux, 5 h.



Scheme 3 *Reagents and conditions*: (i) KOH (1–2 equiv), MeOH, reflux, 20–28 h.

migration.[26] Taking the above into account, dimethoxytriazines **3a** and **3c** were heated at reflux temperature in toluene in the presence of dimethyl sulfate for 24–48 hours to give 1,3-dimethyl-1,3,5-triazines **15a** and **15c** (Scheme 4); again, no by-products were isolated from these reactions.



Scheme 4 *Reagents and conditions*: (i) Me_2SO_4 (1 equiv), toluene, reflux, 24–48 h.

Products **3b**, **11a**,**c** and **13b**,**c** were selected by the National Cancer Institute (NCI) for biological screening on a 60-cell line panel. They were tested initially at a single dose (10 μM), but did not satisfy the predetermined threshold inhibition criteria, and did not progress to the five-dose screen in order to determine their GI_{50} (concentration that causes 50% growth inhibition) values. However, at this concentration (10 μM), chlorotriazines **3b** and **13b** showed modest cellular growth inhibition of leukemia cell lines (**3b**: 38.9% inhibition of SR; **13b**: 33.4% inhibition of K562), of ovarian cancer cell lines (**3b**: 42.7% inhibition of IGROV1 and 43.8% inhibition of OVCAR-8), and of a renal cancer cell line (**13b**: 35.3% inhibition of CAKI-1). All the other tested compounds were devoid of biological activity on tumor cell lines.

In conclusion, the 2-alkyl-3,5-dimethoxy-1,3,5-triazine system represents a rarely encountered heterocyclic scaffold. We have demonstrated that partial or total hydrolysis of the methoxy groups, and a Hilbert–Johnson oxygen to nitrogen migration of the methyl groups can be realized easily by using dilute potassium hydroxide or hydrochloric acid, or by catalysis with dimethyl sulfate. These reactions allowed the preparation of a variety of potential biocides, formed from pyrrolidinones substituted at the 5-position with a triazine scaffold. The antifungal properties of these compounds will be reported in due course.

All starting materials were commercially available. Thin-layer chromatography (TLC) was performed on Macherey Nagel silica gel plates containing a fluorescent indicator, and were made visual under a UV lamp at 254 nm and 366 nm. Column chromatography was accomplished on silica gel (40–60 μm; Macherey Nagel). Melting points were measured on an MPA 100 OptiMelt apparatus and are uncorrected. IR spectra were recorded on a Varian 640-IR FT-IR spectrometer. NMR spectra were acquired at 200 MHz (^{1}H NMR) on a Varian Gemini 2000 spectrometer, or at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) on a Varian 400 MHz Premium Shielded spectrometer. Chemical shifts (δ) are expressed in parts per million relative to TMS as the internal standard. LC–MS was accomplished using an HPLC combined with a Surveyor MSQ (Thermo Electron) equipped with an APCI source. Elemental analysis of new compounds were recorded by 'Pôle Chimie Moléculaire', Faculté de Sciences Mirande, Université de Bourgogne, Dijon, France. Many of the products obtained during this study were difficult to obtain in perfectly anhydrous form; similar problems have been reported previously with triazine compounds.[27]

Methyl *N*-Arylpyroglutamates 9a,b; General Procedure
To a suspension of methyl DL-pyroglutamate (1 equiv), CuI (0.5 equiv), Cs_2CO_3 (2 equiv), and the appropriate aryl halide (1.0–1.5 equiv) in 1,4-dioxane under an N_2 atmosphere was added dropwise the coupling ligand, *N*,*N*′-dimethylethylenediamine (DMEDA) (1 equiv) via a syringe. The mixture was then stirred at 50 °C or 60 °C for 12 or 20 h, turning blue very quickly.[10] After cooling to r.t., the mixture was filtered to remove insoluble salts and the filter cake was washed with CH_2Cl_2. The filtrate was concentrated in vacuo and the residue was partitioned between H_2O and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography on silica gel (EtOAc–*n*-heptane) to afford pure compound **9a** or **9b**.

Methyl *N*-(Benzo[1,3]dioxol-5-yl)pyroglutamate (9a)
The general procedure was followed using methyl DL-pyroglutamate (2.0 g, 14 mmol), 5-bromo-1,3-benzodioxole (2.5 mL, 21 mmol), Cs_2CO_3 (9.1 g, 28 mmol), CuI (1.3 g, 7 mmol) and DMEDA (1.5 mL, 14 mmol) in 1,4-dioxane (40 mL). The mixture was stirred at 60 °C for 12 h. The residue was separated by chromatography on silica gel (EtOAc–*n*-heptane, 3:2) to afford pure product **9a** as a white powder (3.13 g, 85%). The physicochemical properties were identical to those reported in the literature.[10]

Methyl *N*-(4-Acetylphenyl)pyroglutamate (9b)
The general procedure was followed using methyl DL-pyroglutamate (2.91 g, 20.32 mmol), 1-(4-iodophenyl)ethanone (5.00 g, 20.32 mmol), Cs_2CO_3 (13.24 g, 40.64 mmol), CuI (1.96 g, 10.16 mmol) and DMEDA (2.18 mL, 20.32 mmol) in 1,4-dioxane (50 mL). The mixture was stirred at 50 °C for 20 h. The residue was separated by chromatography on silica gel (EtOAc–*n*-heptane, 1:1) to afford pure product **9b**.

Yield: 3.45 g (65%); white solid; mp (EtOAc) 96–99 °C; R_f = 0.23 (EtOAc–*n*-heptane, 1:1).

IR (neat): 1738, 1712, 1669, 1599, 1377, 1346, 1261, 1197, 1177, 840 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.20–2.29 (m, 1 H, CH_2CH_2CH), 2.48–2.56 (m, 1 H, CH_2CH_2CH), 2.58 (s, 3H, $COCH_3$), 2.59–2.64 (m, 1 H, CH_2CH_2CH), 2.72–2.84 (m, 1 H, CH_2CH_2CH), 3.76 (s, 3 H, $COOCH_3$), 4.82 (m, 1 H, CH_2CH_2CH), 7.63 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.96 (d, *J* = 8.8 Hz, 2 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1 (CH_2), 26.5 (CH_3), 31.0 (CH_2), 52.9 (CH_3), 61.0 (CH), 119.8 and 119.9 (2 rotamers, 2 CH), 129.4 and 129.5 (2 rotamers, 2 CH), 133.5 (C), 142.4 (C), 171.9 (C), 174.4 (C), 196.9 (C).

Anal. Calcd for $C_{14}H_{15}NO_4 \cdot 0.2H_2O$: C, 63.48; H, 5.86; N, 5.29. Found: C, 63.76; H, 6.16; N, 5.53.

Pyroglutamic Acids 10a,b; General Procedure
A mixture of ester **9a** or **9b** (1 equiv) and aq NaOH (2 M, 2 equiv) was stirred at 80 °C for 1 or 10 h (until the starting ester had dissolved completely, which was equivalent to sodium carboxylate formation). After cooling to r.t., the stirred soln was acidified to pH 5–6 by slow addition of concd HCl. The solid obtained by filtration was washed with distilled H_2O and dried to give pure acid **10a** or **10b**.

***N*-(Benzo[1,3]dioxol-5-yl)pyroglutamic Acid (10a)**
The general procedure was followed using ester **9a** (0.80 g, 2.59 mmol) and aq NaOH [0.17 g, 4.25 mmol in H_2O (2.2 mL), 2 M]. The mixture was stirred at 80 °C for 10 h. The solid obtained by filtration was washed with H_2O and dried to give acid **10a**.

Yield: 0.75 g (99%); white solid; mp (H_2O) 156–158 °C; R_f = 0.24 (CH_2Cl_2).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.15–2.30 (m, 1 H, CH_2CH_2CH), 2.44–2.81 (m, 3 H, CH_2CH_2CH), 4.63 (dd, *J* = 8.9, 3.1 Hz, 1 H, CH_2CH_2CH), 5.81 (br s, 1 H, COO*H*), 5.96 (s, 2 H, OCH_2O), 6.767 (d, *J* = 2.7 Hz, 1 H, Ar*H*), 6.771 (s, 1 H, Ar*H*), 7.06 (dd, *J* = 1.8, 0.9 Hz, 1 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$–DMSO-d_6): δ = 23.2 (CH_2), 30.6 (CH_2), 62.4 (CH), 101.2 (CH_2), 105.0 (CH), 107.9 (CH), 115.6 (CH), 132.3 (C), 145.3 (C), 147.7 (C), 173.4 (C), 174.4 (C).

Anal. Calcd for $C_{12}H_{11}O_5N$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.57; H, 4.31; N, 5.93.

***N*-(4-Acetylphenyl)pyroglutamic Acid (10b)**
The general procedure was followed using ester **9b** (2.40 g, 9.19 mmol) and aq NaOH [0.73 g, 18.35 mmol in H_2O (9.2 mL), 2 M]. The mixture was stirred at 80 °C for 1 h. The solid obtained by filtration was washed with H_2O and dried to give acid **10b**.

Yield: 1.57 g (69%); white solid; mp (H_2O) 207–210 °C.

IR (neat): 3349, 1707, 1668, 1598, 1581, 1442, 1385, 1328, 1287, 1213, 1186, 1108, 901, 823 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.70–1.82 (m, 1 H, CH_2CH_2CH), 1.83–1.97 (m, 1 H, CH_2CH_2CH), 2.17–2.32 (m, 2 H, CH_2CH_2CH), 2.24 (s, 3 H, $COCH_3$), 6.43 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.59–6.64 (m, 1 H, CH_2CH_2CH), 7.56 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 12.32 (s, 1 H, COOH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.9 (CH_3), 27.5 (CH_2), 30.5 (CH_2), 54.9 (CH), 111.7 (C), 126.0 (2 CH), 130.8 (2 CH), 152.6 (C), 174.2 (C), 174.6 (C), 195.6 (C).

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.97; H, 5.12; N, 5.60.

Acid Chlorides 6a–c and 7a,b; General Procedure
A mixture of carboxylic acid **10a** or **10b** (1 equiv) and $SOCl_2$ (2 equiv) in CH_2Cl_2 was heated at reflux temperature under an inert atm for 2–24 h. The resulting pale yellow soln was concentrated in vacuo to give the crude acid chloride **6a–c**, **7a** or **7b** as a pale yellow solid in quant. yield, which was used without further purification in the subsequent step.

The physicochemical properties of acid chlorides **6a–c** were identical to those reported in the literature.[6]

1-(1,3-Benzodioxol-5-yl)-5-oxoprolyl Chloride (7a)
^1H NMR (400 MHz, $CDCl_3$): δ = 2.35–2.44 (m, 1 H, CH_2CH_2CH), 2.56–2.80 (m, 3 H, CH_2CH_2CH), 4.90–4.97 (m, *J* = 4.7, 2.9, 1.9 Hz, 1 H, CH_2CH_2CH), 5.99 (s, 2 H, OCH_2O), 6.72 (dd, *J* = 8.4, 2.0 Hz, 1 H, Ar*H*), 6.81 (d, *J* = 8.2 Hz, 1 H, Ar*H*), 7.05 (d, *J* = 2.0 Hz, 1 H, Ar*H*).

1-(4-Acetylphenyl)-5-oxoprolyl Chloride (7b)
^1H NMR (400 MHz, $CDCl_3$): δ = 2.22–2.40 (m, 1 H, CH_2CH_2CH), 2.43–2.81 (m, 3 H, CH_2CH_2CH), 2.59 (s, 3 H, $COCH_3$), 4.80 (m, 1 H, CH_2CH_2CH), 7.66 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 8.00 (d, *J* = 8.6 Hz, 2 H, Ar*H*).

Dimethoxytriazines 3a–c and 4a,b; General Procedure
Under an inert atm, a soln of acid chloride **6a–c**, **7a** or **7b** (1 equiv) in anhyd CH_2Cl_2 was added dropwise over 30 min to a stirred mixture of zinc dimethyl imidodicarbonimidate (**5**) (0.5–0.75 equiv) and powdered 4 Å MS in distilled py (15 mL). After the addition was complete, the mixture was stirred at r.t. for 24 h. The mixture was filtered, the solid washed with CH_2Cl_2 and the filtrate concentrated in vacuo. The residue was co-evaporated with toluene (3 × 5 mL) in order to remove py. The remaining slurry was dissolved in CH_2Cl_2 (10 mL), washed with HCl (1 M, 3 × 10 mL), and then aq sat. $NaHCO_3$ soln (10 mL). Following evaporation, the obtained residue was crystallized or purified by column chromatography, then recrystallized from an appropriate solvent to give pure dimethoxytriazine **3a–c**, **4a** or **4b**.

The physicochemical properties of triazines **3a–c** were identical to those reported in the literature.[6]

1-Benzo[1,3]dioxol-5-yl-5-(4,6-dimethoxy[1,3,5]triazin-2-yl)pyrrolidine-2-one (4a)

The general procedure was followed using acid chloride **7a** (0.54 g, 2.02 mmol), zinc derivative **5** (0.50 g, 1.54 mmol), py (20 mL) and CH_2Cl_2 (3 mL) in the presence of powdered 4 Å MS (2.00 g). The residue obtained upon evaporation was purified by column chromatography (EtOAc–*n*-heptane, 7:3) to provide pure triazine **4a**.

Yield: 0.5 g (67%); white solid; mp (EtOAc–*n*-heptane) 114–116 °C; R_f = 0.26 (EtOAc–*n*-heptane, 7:3).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.04–2.20 (m, 1 H, CH_2CH_2CH), 2.52–2.96 (m, 3 H, CH_2CH_2CH), 4.01 (s, 6 H, 2 OCH_3), 5.05–5.12 (m, 1 H, CH_2CH_2CH), 5.92 (s, 2 H, OCH_2O), 6.72 (dd, *J* = 12.7, 8.5 Hz, 2 H, Ar*H*), 7.12 (d, *J* = 1.8 Hz, 1 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1 (CH_2), 30.7 (CH_2), 55.5 (2 CH_3), 65.3 (CH), 101.3 (CH_2), 105.2 (CH), 107.9 (CH), 115.9 (CH), 132.3 (C), 145.2 (C), 147.7 (C), 172.9 (2 C), 174.8 (C), 181.9 (C).

Anal. Calcd for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68; N, 16.27. Found: C, 56.11; H, 4.51; N, 15.90.

1-(4-Acetylphenyl)-5-(4,6-dimethoxy-1,3,5-triazin-2-yl)pyrrolidin-2-one (4b)

The general procedure was followed using acid chloride **7b** (1.64 g, 6.19 mmol), zinc derivative **5** (1.01 g, 3.09 mmol), py (20 mL) and CH_2Cl_2 (3 mL) in the presence of powdered 4 Å MS (3.00 g). The residue obtained upon evaporation was purified by column chromatography on silica gel (EtOAc–*n*-heptane, 7:3) to afford pure compound **4b**.

Yield: 738 mg (35%); white solid; mp (EtOAc) 137–139 °C; R_f = 0.13 (EtOAc–*n*-heptane, 1:1).

IR (neat): 1695, 1678, 1549, 1502, 1457, 1366, 1272, 1257, 1108, 1072, 1025, 932, 831 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14–2.22 (m, 1 H, CH_2CH_2CH), 2.17 (s, 3 H, $COCH_3$), 2.61–2.72 (m, 2 H, CH_2CH_2CH), 2.82–2.95 (m, 1 H, CH_2CH_2CH), 3.99 (s, 6 H, 2 OCH_3), 5.23–5.30 (m, 1 H, CH_2CH_2CH), 7.67 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.89 (d, *J* = 8.4 Hz, 2 H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9 (CH_2), 26.1 (CH_3), 31.2 (CH_2), 55.5 (2 CH_3), 63.1 (CH), 120.0 (2 CH), 129.3 (2 CH), 133.1 (C), 142.7 (C), 172.9 (C), 175.1 (2 C), 181.5 (C), 196.9 (C).

Anal. Calcd for $C_{17}H_{18}N_4O_4 \cdot 0.5H_2O$: C, 58.11; H, 5.45; N, 15.95. Found: C, 58.11; H, 5.49; N, 15.81.

O-Demethylated Derivatives 11a–c and 12a,b; General Procedure

A suspension of dimethoxytriazine **3a**–**c**, **4a** or **4b** (1 equiv) in aq HCl (1.8%, 2 equiv) was heated at reflux temperature for 5 h. After cooling to r.t., the precipitate formed was filtered and washed with H_2O to afford pure triazinedione **11a**–**c**, **12a** or **12b**.

6-[1-(2-Methylbenzyl)-5-oxopyrrolidin-2-yl]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (11a)

The general procedure was followed using dimethoxytriazine **3a** (1.00 g, 3.05 mmol) and HCl (1.8%, 10.5 mL). Pure compound **11a** was obtained after filtration.

Yield: 650 mg (71%); white solid; mp (H_2O) 136–137 °C.

IR (neat): 3500, 3386, 1727, 1686, 1662, 1611, 1433, 1413, 1244, 1156, 953, 905, 795, 540 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.98–2.07 (m, 1 H, CH_2CH_2CH), 2.20 (s, 3 H, $ArCH_3$), 2.25–2.45 (m, 3 H, CH_2CH_2CH), 3.89 (d, *J* = 15.2 Hz, 1 H, $ArCH_2N$), 4.10 (dd, *J* = 8.7, 2.6 Hz, 1 H, CH_2CH_2CH), 4.72 (d, *J* = 15.2 Hz, 1 H, $ArCH_2N$), 7.07 (d, *J* = 7.2 Hz, 1 H, Ar*H*), 7.10–7.18 (m, 3 H, Ar*H*), 11.25 (s, 1 H, CON*H*CN), 12.09 (s, 1 H, CON*H*CO).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.1 (CH_3), 23.9 (CH_2), 29.2 (CH_2), 43.2 (CH_2), 58.5 (CH), 126.3 (CH), 128.0 (CH), 128.9 (CH), 130.7 (CH), 134.4 (2 C), 137.0 (C), 168.9 (2 C), 175.0 (C).

Anal. Calcd for $C_{15}H_{16}N_4O_3 \cdot H_2O$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.19; H, 5.79; N, 17.93.

6-[1-(4-Chlorobenzyl)-5-oxopyrrolidin-2-yl]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (11b)

The general procedure was followed using dimethoxytriazine **3b** (1.00 g, 2.87 mmol) and HCl (1.8%, 8.5 mL). Pure compound **11b** was obtained after filtration.

Yield: 763 mg (83%); white solid; mp (H_2O) 167–169 °C.

IR (neat): 3364, 2945, 1759, 1665, 1611, 1491, 1458, 1394, 1360, 1248, 997, 791 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.03–2.09 (m, 1 H, CH_2CH_2CH), 2.32–2.39 (m, 3 H, CH_2CH_2CH), 4.00 (d, *J* = 15.2 Hz, 1 H, $ArCH_2N$), 4.26 (dd, *J* = 9.2, 3.6 Hz, 1 H, CH_2CH_2CH), 4.77 (d, *J* = 15.6 Hz, 1 H, $ArCH_2N$), 7.28 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.42 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 11.32 (s, 1 H, CON*H*CN), 12.22 (s, 1 H, CON*H*CO).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.7 (CH_2), 29.1 (CH_2), 44.1 (CH_2), 58.6 (CH), 128.9 (2 CH), 130.3 (2 CH), 132.4 (C), 136.1 (2 C), 168.9 (2 C), 175.3 (C).

Anal. Calcd for $C_{14}H_{13}ClN_4O_3 \cdot 1.5H_2O$: C, 48.35; H, 4.64; N, 16.11. Found: C, 48.31; H, 4.25; N, 16.12.

6-[1-(1,3-Benzodioxol-5-ylmethyl)-5-oxopyrrolidin-2-yl]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (11c)

The general procedure was followed using dimethoxytriazine **3c** (0.71 g, 1.95 mmol) and HCl (1.8%, 7.5 mL). Pure compound **11c** was obtained after filtration.

Yield: 548 mg (85%); white solid; mp (H_2O) 219–221 °C.

IR (neat): 3080, 2929, 2760, 1754, 1687, 1658, 1604, 1498, 1455, 1245, 1029, 915, 793, 665, 631, 530 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.95–2.05 (m, 1 H, CH_2CH_2CH), 2.19–2.43 (m, 3 H, CH_2CH_2CH), 3.83 (d, *J* = 14.9 Hz, 1 H, $ArCH_2N$), 4.15 (dd, *J* = 8.5, 2.9 Hz, 1 H, CH_2CH_2CH), 4.65 (d, *J* = 14.9 Hz, 1 H, $ArCH_2N$), 5.97 (dd, *J* = 3.1, 0.8 Hz, 2 H, OCH_2O), 6.67 (dd, *J* = 7.8, 1.6 Hz, 1 H, Ar*H*), 6.77 (d, *J* = 1.6 Hz, 1 H, Ar*H*), 6.83 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 11.27 (s, 1 H, CON*H*CN), 12.14 (s, 1 H, CON*H*CO).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.7 (CH_2), 29.3 (CH_2), 44.5 (CH_2), 58.5 (CH), 101.4 (CH_2), 101.6 (CH), 109.0 (CH), 121.9 (CH), 130.7 (C), 147.0 (C), 148.8 (2 C), 169.0 (C), 175.1 (2 C).

Anal. Calcd for $C_{15}H_{14}N_4O_5$: C, 54.55; H, 4.27; N, 16.96. Found: C, 54.79; H, 4.44; N, 16.99.

6-[1-(Benzo[1,3]dioxol-5-yl)-5-oxopyrrolidin-2-yl]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (12a)

The general procedure was followed using dimethoxytriazine **4a** (0.15 g, 0.44 mmol) and HCl (1.8%, 6 mL). Pure compound **12a** was obtained after filtration.

Yield: 113 mg (81%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.25–2.36 (m, 1 H, CH_2CH_2CH), 2.40–2.63 (m, 3 H, CH_2CH_2CH), 5.00–5.03 (m, 1 H, CH_2CH_2CH), 6.28 (s, 2 H, OCH_2O), 7.08 (dd, *J* = 8.4, 1.9 Hz, 1 H, Ar*H*), 7.17 (d, *J* = 8.4 Hz, 1 H, Ar*H*), 7.45 (d, *J* = 1.9 Hz, 1 H, Ar*H*), 10.15 (s, 1 H, N*H*), 11.61 (s, 1 H, N*H*).

Anal. Calcd for $C_{14}H_{12}N_4O_5$: C, 53.17; H, 3.82; N, 17.71. Found: C, 53.43; H, 4.05; N, 17.40.

6-[1-(4-Acetylphenyl)-5-oxopyrrolidin-2-yl]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (12b)

The general procedure was followed using dimethoxytriazine **4b** (0.26 g, 0.75 mmol) and HCl (1.8%, 10 mL). Pure compound **12b** was obtained after filtration.

Yield: 112 mg (47%); white solid; mp (H_2O) 170–173 °C.

IR (neat): 3547, 3476, 1717, 1677, 1616, 1599, 1421, 1356, 1267, 1222, 1039, 848, 772, 620, 547 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.33–2.40 (m, 1 H, CH_2CH_2CH), 2.58–2.69 (m, 1 H, CH_2CH_2CH), 2.67 (s, 3 H, $COCH_3$), 2.72–2.80 (m, 2 H, CH_2CH_2CH), 5.24 (dd, *J* = 8.4, 2.8 Hz, 1 H, CH_2CH_2CH), 7.79 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 8.09 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 11.49 (s, 1 H, CON*H*CN), 12.66 (s, 1 H, CON*H*CO).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.8 (CH_2), 27.0 (CH_3), 31.0 (CH_2), 60.4 (CH), 119.7 (2 CH), 129.6 (2 CH), 132.9 (C), 142.8 (2 C), 168.6 (C), 175.2 (C), 197.1 (C).

Anal. Calcd for $C_{15}H_{14}N_4O_4 \cdot MeOH \cdot H_2O$: C, 52.74; H, 5.53; N, 15.3. Found: C, 52.79; H, 5.12; N, 15.18.

Mono O-Demethylated Derivatives 13a–c and 14b; General Procedure

Dimethoxytriazine **3a–c** or **4b** (1 equiv) was added to a soln of KOH (1–2 equiv) in MeOH and the resulting mixture heated at reflux temperature for 19–28 h. After cooling to r.t., the solvent was evaporated in vacuo and the residue dissolved in CH_2Cl_2. All insoluble salts were removed by filtration and the filtrate was concentrated in vacuo. Et_2O was then added to the crude residue and the obtained precipitate was collected by filtration to give pure product **13a–c** or **14b**.

6-Methoxy-4-[1-(2-methylbenzyl)-5-oxopyrrolidin-2-yl]-1,3,5-triazin-2(1*H*)-one (13a)

The general procedure was followed using dimethoxytriazine **3a** (0.50 g, 1.52 mmol) and KOH (0.085 g, 1.52 mmol) in MeOH (10 mL). The reaction mixture was heated at reflux temperature for 24 h. The obtained white solid was filtered and dried to provide mono O-demethylated product **13a**.

Yield: 380 mg (80%); yellow solid.

IR (neat): 3080, 2929, 2760, 1754, 1687, 1658, 1604, 1498, 1455, 1245, 1029, 915, 793, 665, 631, 530 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.77–1.90 (m, 1 H, CH_2CH_2CH), 2.12–2.32 (m, 2 H, CH_2CH_2CH), 2.16 (s, 3 H, $ArCH_3$), 2.35–2.45 (m, 1 H, CH_2CH_2CH), 3.67 (s, 3 H, OCH_3), 3.71 (d, *J* = 15.2 Hz, 1 H, $ArCH_2N$), 3.93 (dd, *J* = 8.5, 2.9 Hz, 1 H, CH_2CH_2CH), 4.84 (d, *J* = 15.2 Hz, 1 H, $ArCH_2N$), 6.99 (d, *J* = 7.2 Hz, 1 H, Ar*H*), 7.08–7.18 (m, 3 H, Ar*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.1 (CH_3), 24.6 (CH_2), 29.9 (CH_2), 42.6 (CH_2), 53.2 (CH), 61.8 (CH_3), 126.3 (CH), 127.7 (CH), 128.7 (CH), 130.6 (CH), 135.0 (C), 136.6 (C), 172.2 (C), 175.0 (2 C), 177.8 (C).

LC–MS ($APCI^+$): *m*/*z* 315.1 $[M + H]^+$.

4-[1-(4-Chlorobenzyl)-5-oxopyrrolidin-2-yl]-6-methoxy-1,3,5-triazin-2(1*H*)-one (13b)

The general procedure was followed using dimethoxytriazine **3b** (0.25 g, 0.72 mmol) and KOH (0.040 g, 0.72 mmol) in MeOH (8 mL). The reaction mixture was heated at reflux temperature for 24 h. The obtained white solid was filtered and dried to provide mono O-demethylated product **13b**.

Yield: 209 mg (87%); yellow solid.

IR (neat): 3043, 2756, 1755, 1667, 1489, 1423, 1212, 1088, 915, 799, 672 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.02–2.10 (m, 1 H, CH_2CH_2CH), 2.32–2.45 (m, 2 H, CH_2CH_2CH), 2.61–2.76 (m, 1 H, CH_2CH_2CH), 3.84 (d, *J* = 15.1 Hz, 1 H, $ArCH_2N$), 3.86 (s, 3 H, OCH_3), 4.21 (m, 1 H, CH_2CH_2CH), 4.95 (d, *J* = 15.1 Hz, 1 H, $ArCH_2N$), 7.12 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 7.26 (d, *J* = 8.2 Hz, 2 H, Ar*H*).

Anal. Calcd for $C_{15}H_{15}ClN_4O_3$: C, 53.82; H, 4.52; N, 16.74. Found: C, 54.12; H, 4.80; N, 17.01.

4-[1-(1,3-Benzodioxol-5-ylmethyl)-5-oxopyrrolidin-2-yl]-6-methoxy-1,3,5-triazin-2(1*H*)-one (13c)

The general procedure was followed using dimethoxytriazine **3c** (0.50 g, 1.40 mmol) and KOH (0.156 g, 2.79 mmol) in MeOH (10 mL). The reaction mixture was heated at reflux temperature for 28 h. The obtained white solid was filtered and dried to provide mono O-demethylated product **13c**.

Yield: 350 mg (73%); yellow solid; mp (Et_2O) 230–232 °C.

IR (neat): 2955, 1663, 1560, 1489, 1444, 1363, 1242, 1203, 1099, 1035, 835, 772, 650 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.79–1.90 (m, 1 H, CH_2CH_2CH), 2.13–2.29 (m, 2 H, CH_2CH_2CH), 2.31–2.42 (m, 1 H, CH_2CH_2CH), 3.58 (d, *J* = 14.9 Hz, 1 H, $ArCH_2N$), 3.56 (s, 3 H, OCH_3), 3.99 (dd, *J* = 8.6, 3.2 Hz, 1 H, CH_2CH_2CH), 4.73 (d, *J* = 14.9 Hz, 1 H, $ArCH_2N$), 5.97 (s, 2 H, OCH_2O), 6.60 (dd, *J* = 7.8, 1.5 Hz, 1 H, Ar*H*), 6.70 (d, *J* = 1.5 Hz, 1 H, Ar*H*), 6.81 (d, *J* = 7.8 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.4 (CH_2), 30.0 (CH_2), 44.4 (CH_2), 53.2 (CH), 61.8 (CH_3), 101.3 (CH_2), 108.6 (CH), 108.7 (CH), 121.5 (CH), 131.2 (C), 146.8 (C), 147.8 (C), 172.1 (C), 175.1 (2C), 177.4 (C).

LC–MS ($APCI^+$): *m*/*z* 345.1 $[M + H]^+$.

4-[1-(4-Acetylphenyl)-5-oxopyrrolidin-2-yl]-6-methoxy-1,3,5-triazin-2(1*H*)-one (14b)

The general procedure was followed using dimethoxytriazine **4b** (0.35 g, 1.02 mmol) and KOH (0.114 g, 2.04 mmol) in MeOH (10 mL). The reaction mixture was heated at reflux temperature for 19 h. The obtained white solid was filtered and dried to provide mono O-demethylated product **14b**.

Yield: 208 mg (62%); yellow solid.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.18–2.24 (m, 1 H, CH_2CH_2CH), 2.45–2.68 (m, 3 H, CH_2CH_2CH), 3.43 (s, 3 H, $COCH_3$), 3.58 (s, 3 H, OCH_3), 4.97–5.02 (m, 1 H, CH_2CH_2CH), 7.70 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 7.91 (d, *J* = 8.2 Hz, 2 H, Ar*H*).

LC–MS ($APCI^+$): *m*/*z* 329.1 $[M + H]^+$.

Hilbert–Johnson Transposition; General Procedure

A soln of dimethoxytriazine **3a** or **3c** (1 equiv) and Me_2SO_4 (1 equiv) in toluene was heated at reflux temperature for 23 or 48 h. After cooling to r.t., the mixture was concentrated in vacuo and the crude residue was treated with Et_3N (1 equiv) and H_2O. The organic compounds were extracted into CH_2Cl_2. After evaporation of the solvent, the resulting solid was recrystallized from absolute EtOH to afford the pure product **15a** or **15c**.

1,3-Dimethyl-6-[1-(2-methylbenzyl)-5-oxopyrrolidin-2-yl]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (15a)

The general procedure was followed using dimethoxytriazine **3a** (0.72 g, 2.20 mmol) and Me_2SO_4 (0.28 g, 2.20 mmol) in toluene (15 mL). The mixture was heated at reflux temperature for 23 h. After recrystallization, the obtained white precipitate was filtered to provide pure product **15a**.

Yield: 374 mg (52%); yellow solid; mp (EtOH) 113–116 °C.

IR (neat): 1727, 1655, 1591, 1453, 1417, 1365, 1287, 1238, 1160, 986, 788, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.92–2.01 (m, 1 H, CH_2CH_2CH), 2.27 (s, 3 H, $ArCH_3$), 2.36–2.58 (m, 2 H, CH_2CH_2CH), 2.64–2.68 (m, 1 H, CH_2CH_2CH), 3.10 (s, 3 H, NCH_3), 3.36 (s, 3 H, NCH_3), 4.15 (d, *J* = 14.4 Hz, 1 H, $ArCH_2N$), 4.28 (dd, *J* = 9.0, 3.1 Hz, 1 H,

CH_2CH_2CH), 4.99 (d, J = 14.8 Hz, 1 H, $ArCH_2N$), 6.96 (d, J = 7.2 Hz, 1 H, Ar*H*), 7.09–7.12 (m, 1 H, Ar*H*), 7.15–7.22 (m, 2 H, Ar*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.1 (CH_3), 22.9 (CH_2), 28.9 (CH_3), 29.0 (CH_2), 31.0 (CH_3), 43.3 (CH_2), 57.5 (CH), 126.2 (CH), 127.8 (CH), 128.6 (CH), 130.6 (CH), 134.7 (C), 136.9 (C), 151.7 (C), 154.7 (C), 166.5 (C), 175.1 (C).

Anal. Calcd for $C_{17}H_{20}N_4O_3 \cdot H_2O$: C, 58.95; H, 6.40; N, 16.17. Found: C, 58.92; H, 6.41; N, 15.76.

6-[1-(1,3-Benzodioxol-5-ylmethyl)-5-oxopyrrolidin-2-yl]-1,3-dimethyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (15c)

The general procedure was followed using dimethoxytriazine **3c** (0.69 g, 1.90 mmol) and Me_2SO_4 (0.24 g, 1.90 mmol) in toluene (15 mL). The reaction mixture was heated at reflux temperature for 48 h. After recrystallization, the obtained white precipitate was filtered to provide pure product **15c**.

Yield: 212 mg (46%); yellow solid; mp (EtOH) 167–169 °C.

IR (neat): 1730, 1658, 1593, 1489, 1441, 1366, 1282, 1246, 1162, 1031, 919, 789 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.98–2.15 (m, 1 H, CH_2CH_2CH), 2.22–2.34 (m, 2 H, CH_2CH_2CH), 2.35–2.40 (m, 1 H, CH_2CH_2CH), 3.16 (s, 3 H, NCH_3), 3.23 (s, 3 H, NCH_3), 3.77 (d, J = 14.8 Hz, 1 H, $ArCH_2N$), 4.67 (d, J = 14.4 Hz, 1 H, $ArCH_2N$), 4.67 (d, J = 9.6 Hz, 1 H, CH_2CH_2CH), 5.96 (s, 2 H, OCH_2O), 6.72–6.74 (m, 1 H, Ar*H*), 6.81–6.84 (m, 2 H, Ar*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.3 (CH_2), 28.9 (CH_3), 29.0 (CH_2), 31.1 (CH_3), 44.7 (CH_2), 57.5 (CH), 101.4 (CH_2), 108.6 (CH), 109.0 (CH), 121.9 (CH), 131.2 (C), 146.9 (C), 147.8 (C), 151.8 (C), 154.8 (C), 166.6 (C), 175.2 (C).

Anal. Calcd for $C_{17}H_{18}N_4O_5 \cdot 1.5H_2O$: C, 52.57; H, 5.54; N, 14.43. Found: C, 52.59; H, 5.10; N, 14.18.

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