Heterocyclic synthesis using nitrilimines. Part 11. Synthesis of 1-aryl-3-phenylaminocarbonyl-4,5-dihydro-1,4,5-triazin-6-ones

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Abstract
1-Aryl-3-phenylaminocarbonyl-4,5-dihydro-1,4,5-triazin-6-ones were prepared from the reaction of C-phenylaminocarbonyl-N-arylnitrilimines with α-amino acid methyl esters. Some of these compounds were tested for antitumor activity.

Keywords: Nitrilimines, α-amino acid methyl esters, cyclocondensation, 4,5-dihydro-1,2,4-triazinones

Introduction
The reaction of 1,3-dipoles with nucleophiles incorporating a suitably located electrophilic center represents a good method for the synthesis of five-, six- or seven-membered heterocycles depending on the reacting species.1 Nitrile oxides and nitrilimines are reported to react with α-amino esters to form 4,5-dihydro-1,2,4-oxadiazin-6-ones and 4,5-dihydro-1,2,4-triazin-6-ones respectively.2-6 Several reports revealed that 1,2,4-triazinone derivatives possess significant biological activities, such as antimicrobial, antibacterial, fungicide, pesticide, herbicide and crop protection, as well as blood platelet aggregation-inhibition.7-12 Researchers have also reported that some substituted 1,2,4-triazin-6-ones possess antitumoral activity against leukemia, ovarian cancer, small and large lung cancer cells, and breast cancer.13-17 Recently, 1,2,4-triazinones have received significant attention as ligands to transition metals. The reaction of 1,3,5-trisubstituted 4,5-dihydro-1,2,4-triazine oximes with metal acetates afforded various complexes according to the reagent and conditions used.18-20 As part of our program aimed at developing new biologically active compounds, we report here the synthesis of 1-aryl-3-phenylaminocarbonyl-
4,5-dihydro-1,2,4-triazin-6-ones from the reaction of C-phenylamino-carbonyl-N-arylnitrilimines with various α-amino acid methyl esters.

**Results and Discussion**

The reaction of α-amino esters with nitrilimines was first explored by El-Abadelah in 1991. In the present study, the nitrilimines 1a-e, generated *in situ* from the respective hydrazonoyl chlorides 2a-e, are found to react with α-amino ester hydrochlorides 3a-e at low temperature in the presence of triethylamine to give six-membered heterocycles, 4,5-dihydro-1,2,4-triazin-6-ones 5-9a-e (Scheme 1). The formation of these 1,2,4-triazinones can be considered to involve an initial nucleophilic addition of an α-amino esters to the nitrilimine yielding the open-chain amidrazone ester intermediate 4, which cyclizes to produce 4,5-dihydro-1,2,4-triazinones 5-9a-e with the elimination of methanol. According to Baldwin, this type of cyclization is classified as an allowed 6-exo-trig process.21

![Scheme 1. Synthetic pathway to 1,2,4-triazin-6-ones 5-9a-e.](image)

The assignment of structures 5-9a-e is based on their analytical and spectroscopic data. Physical properties, molecular ion peaks and elemental analysis are presented in the Experimental Section. No investigations were carried out concerning optical purity and activity.
Spectroscopic data analysis

The IR spectra of compounds 5-9a-e in KBr revealed the presence of two NH absorption bands in the region 3380-3200 cm\(^{-1}\). The lactam C=O appeared in the region 1690-1660 cm\(^{-1}\), and the amide C=O at about 1650 cm\(^{-1}\). The C=N stretching band appeared in the region 1600-1590 cm\(^{-1}\). The structure of compounds 5-9a-e is also supported by \(^1\)H NMR measurements as follows: for compounds containing a glycine residue, methylene protons appeared as a singlet in the range of 4.3-4.2 ppm. Two NH signals appeared as singlets at 10 ppm and at 6.2 ppm, in addition to the signals of aromatic protons. For those compounds containing an alanine residue, methyl protons appeared as doublets in the range of 1.6-1.5 ppm. The methinyl proton appeared as a quartet in the range of 4.4-4.3 ppm, in addition to the signals of NH and aromatic protons. Compounds 5-9c containing a phenyl glycine residue, the methinyl proton appeared as a singlet in the range of 5.4-5.3 ppm. Two NH signals appeared as singlets at 9.0 ppm and at 6.5 ppm, in addition to the signals resulting from the protons of the aromatic rings. Compounds 5-9d containing a valine residue, had methyl proton signals as a doublet in the range 1.1-0.9 ppm, a methinyl proton as a multiplet in the range of 2.5-2.3 ppm, and the ring methinyl proton as a doublet in the range of 4.2-4.1 ppm. The NH signals appeared at 9.0 and 6.3 ppm in addition to the signals of aromatic protons. Compounds 5-9e containing phenyl alanine residue, has methylene protons of the benzyl group as a doublet in the range 3.2-3.1 ppm. The methinyl proton appeared as a triplet in the range of 4.5-4.3 ppm, in addition to the signals of NH and aromatic protons. The entire \(^1\)H NMR data are presented in the Experimental Section.

The \(^1^3\)CNMR spectra of compounds 5-9a-e displayed the characteristic signals of the suggested structures. The signal of the carbonyl carbon of the amide group appeared in the range of 156-158 ppm, and that of the lactam resonated in the range of 159-162 ppm. The signal at about 139 ppm, is attributed to C=N of the triazinone ring.

The electron impact (EI) mass spectra of compounds 5-9a-e displayed the correct molecular ions in accordance with the suggested molecular formulas. A main fragmentation mode of the closely related substituted 4,5-dihydro-1,2,4-triazin-6-ones was reported to involve hetero ring-scission at the dotted lines as shown below (Scheme 2), leading to fragment ion M-105 as a base peak. The spectra also displayed a significant ion corresponding to M-29. This ion might originate via expulsion of (HC=O) from the molecular ion. The mass spectra of compounds 5-9a showed base peaks at 294, 328, 373, 312 and 308, respectively. The base peak for compounds 5-9b (alanine rest) is M-43, for compounds 5-9c (phenyl glycine rest) at M-105, for compounds 5-9d (valine rest) at M-71 and the base peak for compounds 5-9e (phenylalanine rest) was at M-119.
Antitumor activity
The antitumor activity of some of the newly synthesized compounds was studied against human cancer cell lines HT-29 (colon cancer cell), MCF-7 (breast cancer cell) and MDA (leukemia cell) using the method reported by Ott et al. The incubation time for HT-29 was 48 hours, for MCF-7 96 hours, for MDA 72 hours and for the other compounds, three days at human body temperature. IC\textsubscript{50} values which determined as that concentration causing inhibition of cell proliferation were calculated and found for compound 5c is 1.8 µM and for compound 5e is 29.2 µM. Further pharmacological studies for other compounds are ongoing.

Experimental Section

General Procedures. All melting points were measured on an Electrothermal Melting point apparatus, and are uncorrected. The infrared spectra were recorded in potassium bromide (KBr) on a Perkin-Elmer 237FT infrared spectrophotometer. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded in CDCl\textsubscript{3} and DMSO-d\textsubscript{6} on Bruker AM 300 MHz and Jeol LA-300 instruments at 21 °C, using tetramethylsilane (TMS) as an internal reference. Electron impact (EI) mass spectra were measured on Finnigan MAT 8200 and 8400 Mass spectrometers at 70 eV. Elemental analysis were carried out at the microanalytical laboratory, University of Cairo, Giza, Egypt. The hydrazonoyl chlorides 1a-e\textsuperscript{23,26,27} and α-amino ester hydrochlorides 3a-e\textsuperscript{3} were prepared following reported procedures.

General experimental procedure
To a stirred solution of the appropriate hydrazonoyl halides (0.01 mol) in tetrahydrofuran (100 ml) was added a solution of the particular α-amino ester hydrochloride (0.015 mol) in methanol (40 ml). To the resulting reaction mixture, cooled in an ice-salt bath (-5-0 °C), was dropwise added triethylamine (0.05 mol). After addition was complete, stirring was continued for 2 hours
at 0 °C, and then at room temperature for 12 hours. The solvent was removed under reduced pressure, and the residue was washed with water. The resulting solid product was collected and recrystallized from aqueous ethanol to give the desired triazinones.

The following compounds were prepared using this method:

1-Phenyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (5a). Yield 81%, m.p. 168-170 ºC. IR (KBr): cm⁻¹ 3360, 3262 (NH), 1672 (lactam C=O), 1645 (amide C=O), 1590 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.83 (s, 1H, PhNH), 7.58-7.14 (m, 10H, aromatic protons), 6.33 (s, 1H, NH), 4.24 (s, 2H, CH₂); ¹³C NMR (CDCl₃): δ/ppm 160.33 (lactam C=O), 157.10 (amide C=O), 139.34 (C=N), 140.96, 136.92, 129.51, 129.19, 128.78, 127.31, 125.10, 119.87 (8 aromatic carbons), 43.77 (CH₂). MS: m/z = 294 [M⁺]. Anal for C₁₆H₁₄N₄O₂ (294.32) (% Calcd./found) C, 65.30/65.50; H, 4.79/5.13; N, 19.04/19.06.

5-Methyl-1-phenyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (5b). Yield 68%, m.p. 215-217 ºC. IR (KBr): cm⁻¹ 3355, 3253 (NH), 1676 (lactam C=O), 1647 (amide C=O), 1591 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.83 (s, 1H, PhNH), 8.96-7.14 (m, 9H, aromatic protons), 6.31 (s, 1H, NH), 4.37-4.32 (q, 1H, CH, J = 6.7 Hz), 1.58-1.56 (d, 3H, CH₃, J = 6.7 Hz); ¹³C NMR (CDCl₃): δ/ppm 160.25 (lactam C=O), 157.3 (amide C=O), 139.31 (C=N), 140.94, 136.91, 129.48, 129.18, 128.73, 127.21, 125.14, 119.88 (8 aromatic carbons), 49.62 (CH), 19.67 (CH₃). MS: m/z = 308 [M⁺]. Anal for C₁₇H₁₆N₄O₂ (308.34) (% Calcd./found) C, 66.22/66.41; H, 5.23/5.12; N, 18.17/18.04.

1,5-Diphenyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (5c). Yield 75%, m.p. 180-182 ºC. IR (KBr): cm⁻¹ 3360, 3267 (NH), 1672 (lactam C=O), 1647 (amide C=O), 1591 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.80 (s, 1H, PhNH), 7.78-7.24 (m, 15H, aromatic protons), 6.72 (s, 1H, NH), 5.35 (s, 1H, CH); ¹³C NMR (CDCl₃): δ/ppm 160.72 (lactam C=O), 157.70 (amide C=O), 139.00 (C=N), 141.08, 138.63, 138.10, 136.30, 132.55, 129.18, 129.11, 129.06, 128.69, 126.61, 125.08, 119.82 (12 aromatic carbons), 57.31 (CH). MS: m/z = 370 [M⁺]. Anal for C₂₂H₁₈N₄O₂ (370.41) (% Calcd./found) C, 71.34/71.38; H, 4.90/4.71; N, 15.13/15.00.

5-Isopropyl-1-phenyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (5d). Yield 70%, m.p. 158-160 ºC. IR (KBr): cm⁻¹ 3376, 3273 (NH), 1679 (lactam C=O), 1657 (amide C=O), 1601 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.83 (s, 1H, PhNH), 7.81-7.24 (m, 15H, aromatic protons), 6.72 (s, 1H, NH), 5.35 (s, 1H, CH); ¹³C NMR (CDCl₃): δ/ppm 161.37 (lactam C=O), 157.37 (amide C=O), 138.70 (C=N), 140.08, 138.63, 138.10, 136.30, 132.55, 129.18, 129.11, 129.06, 128.69, 126.61, 125.08, 119.82 (12 aromatic carbons), 57.31 (CH). MS: m/z = 396 [M⁺]. Anal for C₁₉H₂₀N₄O₂ (396.40) (% Calcd./found) C, 71.34/71.38; H, 5.99/5.92; N, 16.65/16.42.

5-Benzyl-1-phenyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (5e). Yield 68%, m.p. 158-160 ºC. IR (KBr): cm⁻¹ 3376, 3273 (NH), 1679 (lactam C=O), 1657 (amide C=O), 1601 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.83 (s, 1H, PhNH), 7.81-7.24 (m, 15H, aromatic protons), 6.55 (s, 1H, NH), 4.16-4.15 (d, 1H, CH, J = 6 Hz), 2.56-2.38 (m, 1H, CH), 1.07-1.0 (d, 6H, 2CH₃, J = 6.8 Hz); ¹³C NMR (CDCl₃): δ/ppm 160.13 (lactam C=O), 157.37 (amide C=O), 138.70 (C=N), 140.69, 136.52, 129.17, 128.75, 127.25, 125.24, 125.03, 119.79 (8 aromatic carbons), 59.11 (CH), 32.89 (CH), 18.29, 16.66 (2 CH₃). MS: m/z = 336 [M⁺]. Anal for C₁₉H₂₀N₄O₂ (336.40) (% Calcd./found) C, 67.84/68.04; H, 5.99/5.92; N, 16.65/16.42.
aromatic carbons), 55.30 (CH), 40.18 (CH$_2$). MS: $m/z = 384$ [M$^+$]. Anal for C$_{23}$H$_{20}$N$_4$O$_2$ (384.44) (% Calcd./found): C, 71.86/71.52; H, 5.24/5.1; N, 14.57/14.19.

1-(4-Chlorophenyl)-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (6a). Yield 91%, m.p. 185-187 °C. IR (KBr): cm$^{-1}$ 3387, 3291 (NH), 1682 (lactam C=O), 1655 (amide C=O), 1601 (C=N); $^1$H NMR (CDCl$_3$): $\delta$/ppm 8.80 (s, 1H, PhNH), 7.60-7.20 (m, 9H, aromatic protons), 6.39 (s, 1H, NH); $^{13}$C NMR (CDCl$_3$): $\delta$/ppm 158.50 (lactam C=O), 156.74 (amide C=O), 139.04 (C=N), 138.78, 136.36, 132.51, 129.23, 128.84, 126.17, 125.22, 119.90 (8 aromatic carbons), 43.72 (CH$_2$). MS: $m/z = 328/330$ [M$^+$]. Anal for C$_{16}$H$_{13}$N$_4$O$_2$ (328.76) (% Calcd./found): C, 58.46/58.57; H, 3.99/3.84; N, 17.04/16.94.

1-(4-Chlorophenyl)-5-methyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (6b). Yield 70%, m.p. 158-160 °C. IR (KBr): cm$^{-1}$ 3358, 3264 (NH), 1683 (lactam C=O), 1660 (amide C=O), 139.60 (C=N), 137.65, 134.57, 132.10, 129.21, 128.83, 128.77, 126.21, 119.87 (8 aromatic carbons), 49.88 (CH), 19.85 (CH$_3$). MS: $m/z = 342/344$ [M$^+$]. Anal for C$_{17}$H$_{15}$N$_4$O$_2$ (342.79) (% Calcd./found): C, 59.57/59.82; H, 4.41/4.23; N, 16.34/16.09.

1-(4-Chlorophenyl)-5-phenyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (6c). Yield 73%, m.p. 190-192 °C. IR (KBr): cm$^{-1}$ 3375, 3273 (NH), 1679 (lactam C=O), 1662 (amide C=O), 139.75 (C=N), 138.63, 138.10, 136.30, 129.24, 129.16, 129.05, 128.75, 126.83, 126.05, 125.40, 119.75 (12 aromatic carbons), 57.74 (CH). MS: $m/z = 404/406$ [M$^+$]. Anal for C$_{22}$H$_{17}$ClN$_4$O$_2$ (404.86) (% Calcd./found): C, 65.27/65.54; H, 4.23/4.13; N, 13.84/13.69.

5-Benzyl-1-(4-chlorophenyl)-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (6e). Yield 90%, m.p. 270-272 °C. IR (KBr): cm$^{-1}$ 3356, 3253 (NH), 1678 (C=O lactam), 1652 (amide C=O), 1597 (C=N); $^1$H NMR (CDCl$_3$): $\delta$/ppm 8.58 (s, 1H, PhNH), 7.55-7.14 (m, 14H, aromatic protons), 6.24 (s, 1H, NH), 4.54-4.51 (t, 1H, CH, J = 6 Hz); $^{13}$C NMR (CDCl$_3$): $\delta$/ppm 160.75 (lactam C=O), 157.37 (amide C=O), 138.70 (C=N), 140.69, 136.52, 129.17, 128.75, 127.25, 125.24, 125.03, 119.79, (8 aromatic carbons), 59.11(CH), 32.89 (CH), 18.29, 16.66 (2 CH$_3$). MS: $m/z = 370/372$ [M$^+$]. Anal for C$_{19}$H$_{19}$ClN$_4$O$_2$ (370.84) (% Calcd./found): C, 61.54/61.48; H, 5.16/5.12; N, 15.11/15.37.
aromatic carbons), 55.26 (CH), 40.21 (CH$_2$). MS: $m/z$ = 418/420 [M$^+$]. Anal for C$_{23}$H$_{19}$ClN$_4$O$_2$ (418.89) (% Calcd./found): C; 65.95/65.55; H, 4.57/4.70; N, 13.38/13.68.

1-(4-Bromophenyl)-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (7a). Yield 65%, m.p. 198-200 °C. IR (KBr): cm$^{-1}$ 3349, 3236 (NH), 1685 (lactam C=O), 1654 (amide C=O), 1590 (C=N); $^1$H NMR (CDCl$_3$): δ/ppm 9.99 (s, 1H, PhNH), 7.89-7.11 (m, 9H, aromatic protons), 6.12 (s, 1H, NH), 4.10 (s, 2H, CH$_2$); $^{13}$C NMR (CDCl$_3$): δ/ppm 159.30 (lactam C=O), 157.94 (amide C=O), 139.77 (C=N), 140.42, 137.44, 130.98, 128.65, 126.58, 124.51, 120.95, 118.37 (8 aromatic carbons), 43.51 (CH$_2$). MS: $m/z$ = 373/375 [M$^+$]. Anal for C$_{16}$H$_{13}$BrN$_4$O$_2$ (373.21) (% Calcd./found): C, 51.49/51.49; H, 3.51/3.51; N, 15.01/15.81.

1-(4-Bromophenyl)-5-methyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (7b). Yield 67%, m.p. 170-172 °C. IR (KBr): cm$^{-1}$ 3371, 3269 (NH), 1681 (lactam C=O), 1657 (amide C=O), 1598 (C=N); $^1$H NMR (CDCl$_3$): δ/ppm 10.02 (s, 1H, PhNH), 8.00-7.11 (m, 9H, aromatic protons), 6.12 (s, 1H, NH), 4.24-4.20 (q, 1H, CH, J = 6.7 Hz), 1.41-1.40 (d, 3H, CH$_3$, J = 6.7 Hz); $^{13}$C NMR (CDCl$_3$): δ/ppm 162.43 (lactam C=O), 158.02 (amide C=O), 139.88 (C=N), 140.32, 137.45, 131.04, 128.66, 126.60, 124.44, 120.87, 118.49 (8 aromatic carbons), 48.92 (CH), 19.10 (CH$_3$). MS: $m/z$ = 387/389 [M$^+$]. Anal for C$_{17}$H$_{15}$BrN$_4$O$_2$ (387.24) (% Calcd./found): C, 52.73/53.08; H, 3.90/3.70; N, 14.47/14.42.

1-(4-Bromophenyl)-5-phenyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (7c). Yield 73%, m.p. 182-183 °C. IR (KBr): cm$^{-1}$ 3366, 3271 (NH), 1677 (lactam C=O), 1658 (amide C=O), 1601 (C=N); $^1$H NMR (CDCl$_3$): δ/ppm 10.15 (s, 1H, PhNH), 7.81-7.12 (m, 14H, aromatic protons), 6.12 (s, 1H, NH), 5.25 (s, 1H, CH); $^{13}$C NMR (CDCl$_3$): δ/ppm 159.90 (lactam C=O), 158.00 (amide C=O), 139.80 (C=N), 140.13, 139.56, 137.49, 131.18, 128.80, 128.68, 128.20, 129.56, 124.61, 120.83, 120.23, 118.75 (12 aromatic carbons), 56.66 (CH). MS: $m/z$ = 449/451 [M$^+$]. Anal for C$_{22}$H$_{17}$BrN$_4$O$_2$ (449.31) (% Calcd./found): C, 58.81/59.18; H, 3.81/3.83; N, 12.47/12.69.

1-(4-Bromophenyl)-5-isopropyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (7d). Yield 60%, m.p. 260-262 °C. IR (KBr): cm$^{-1}$ 3349, 3264 (NH), 1685 (lactam C=O), 1661 (amide C=O), 1596 (C=N); $^1$H NMR (CDCl$_3$): δ/ppm 10.38 (s, 1H, PhNH), 7.83-7.16 (m, 9H, aromatic protons), 6.12 (s, 1H, NH), 4.16-4.15 (d, 1H, CH, J = 6 Hz), 2.56-2.38 (m, 1H, CH), 1.07-1.02 (d, 6H, 2CH$_3$, J = 6.8 Hz); $^{13}$C NMR (CDCl$_3$): δ/ppm 161.37 (lactam C=O), 157.37 (amide C=O), 138.70 (C=N), 140.69, 136.52, 129.17, 128.75, 127.25, 125.24, 125.03, 119.79 (8 aromatic carbons), 59.11 (CH), 32.89 (CH), 18.29, 16.66 (2 CH$_3$). MS: $m/z$ = 415/417 [M$^+$]. Anal for C$_{19}$H$_{19}$BrN$_4$O$_2$ (415.29) (% Calcd./found): C, 54.95/54.43; H, 4.61/4.99; N, 13.94/13.36.

5-Benzyl-1-(4-bromophenyl)-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (7e). Yield 65%, m.p. 245-247 °C. IR (KBr): cm$^{-1}$ 3361, 3253 (NH), 1678 (C=O lactam), 1653 (amide C=O), 1602 (C=N); $^1$H NMR (CDCl$_3$): δ/ppm 8.63 (s, 1H, PhNH), 7.55-7.13 (m, 9H, aromatic protons), 6.25 (s, 1H, NH), 4.53-4.51 (t, 1H, CH, J = 6 Hz), 3.22-3.13 (d, 2H, CH$_2$, J = 8.4 Hz); $^{13}$C NMR (CDCl$_3$): δ/ppm 160.78 (lactam C=O), 157.76 (amide C=O), 139.10 (C=N), 140.03, 136.45, 135.19, 129.71, 129.15, 128.92, 128.72, 127.48, 127.32, 125.22, 125.02, 119.83 (12
aromatic carbons), 55.30 (CH), 40.18 (CH2). MS: m/z = 463/465 [M⁺]. Anal for C23H19BrN4O2 (463.34) (% Calcd./found): C, 59.62/59.69; H, 4.13/4.04; N, 12.09/11.68.

1-(4-Fluorophenyl)-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (8a). Yield 63%, m.p. 234-236 °C. IR (KBr): cm⁻¹ 3348, 3240 (NH), 1674 (lactam C=O), 1655 (amide C=O), 1594 (C=N); ¹H NMR (CDCl₃): δ/ppm 9.99 (s, 1H, PhNH), 7.85-7.10 (m, 9H, aromatic protons), 6.12 (s, 1H, NH); ¹³C NMR (CDCl₃): δ/ppm 159.21 (lactam C=O), 157.98 (amide C=O), 139.15 (C=N), 140.02, 136.91, 128.62, 126.81, 124.37, 120.89, 115.00, 114.75 (8 aromatic carbons), 43.22 (CH2). MS: m/z = 463 [M⁺]. Anal for C16H13FN4O2 (312.31) (% Calcd./found): C, 61.54/61.90; H, 4.20/4.05; N, 17.94/17.87.

1-(4-Fluorophenyl)-5-methyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (8b). Yield 63%, m.p. 158-160 °C. IR (KBr): cm⁻¹ 3366, 3244 (NH), 1672 (lactam C=O), 1657 (amide C=O), 1590 (C=N); ¹H NMR (CDCl₃): δ/ppm 10.13 (s, 1H, PhNH), 7.74-7.11 (m, 9H, aromatic protons), 6.12 (s, 1H, NH), 4.25-4.23 (q, 1H, CH, J = 6.7 Hz), 1.55-1.53 (d, 3H, CH₃, J = 6.7 Hz); ¹³C NMR (CDCl₃): δ/ppm 159.79 (lactam C=O), 157.84 (amide C=O), 139.67 (C=N), 140.25, 137.71, 136.54, 128.79, 126.54, 120.95, 115.14, 114.75 (8 aromatic carbons), 48.72 (CH), 19.23 (CH₃). MS: m/z = 326 [M⁺]. Anal for C17H15FN4O2 (326.33) (% Calcd./found): C, 62.75/62.19; H, 4.64/4.30; N, 17.17/17.32.

1-(4-Fluorophenyl)-5-phenyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (8c). Yield 69%, m.p. 240-236 °C. IR (KBr): cm⁻¹ 3371, 3265 (NH), 1679 (lactam C=O), 1651 (amide C=O), 1596 (C=N); ¹H NMR (CDCl₃): δ/ppm 10.13 (s, 1H, PhNH), 7.80-7.11 (m, 14H, aromatic protons), 6.12 (s, 1H, NH), 5.24 (s, 1H, CH); ¹³C NMR (CDCl₃): δ/ppm 159.83 (lactam C=O), 158.05 (amide C=O), 139.96 (C=N), 140.62, 137.51, 136.90, 128.790, 128.67, 128.29, 126.96, 126.55, 124.45, 120.95, 115.14, 114.92 (12 aromatic carbons), 56.72 (CH). MS: m/z = 388 [M⁺]. Anal for C22H17FN4O2 (388.40) (% Calcd./found): C, 68.03/67.94; H, 4.41/4.67; N, 14.42/14.49.

1-(4-Fluorophenyl)-5-isopropyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (8d). Yield 79%, m.p. 288-290 °C. IR (KBr): cm⁻¹ 3382, 3252 (NH), 1683 (lactam C=O), 1654 (amide C=O), 1601 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.83 (s, 1H, PhNH), 7.76-7.14 (m, 9H, aromatic protons), 6.35 (s, 1H, NH), 4.16-4.15 (d, 1H, CH, J = 6 Hz), 2.56-2.38 (m, 1H, CH), 1.07-1.02 (d, 6H, 2CH₃, J = 6.8 Hz); ¹³C NMR (CDCl₃): δ/ppm 161.37 (lactam C=O), 157.37 (amide C=O), 138.70 (C=N), 140.69, 136.52, 129.17, 128.75, 127.25, 125.24, 125.03, 119.79, 8 (aromatic carbons), 59.11 (CH), 32.89 (CH₂), 18.29, 16.66 (2 CH₃). MS: m/z = 354 [M⁺]. Anal for C19H19FN4O2 (354.39) (% Calcd./found): C, 64.40/64.77; H, 5.40/5.00; N, 14.42/14.49.

5-Benzyl-1-(4-fluorophenyl)-3-phenylaminocarbonyl-4,5-di-hydro-1,2,4-triazin-6-one (8e). Yield 70%, m.p. 206-208 °C. IR (KBr): cm⁻¹ 3382, 3252 (NH), 1680 (C=O lactam), 1651 (amide C=O), 1597 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.63 (s, 1H, PhNH), 7.55-7.13 (m, 14H, aromatic protons), 6.25 (s, 1H, NH), 4.53-4.51 (t, 1H, CH, J = 6 Hz), 3.22-3.13 (d, 2H, CH₂, J = 8.4 Hz); ¹³C NMR (CDCl₃): δ/ppm 160.78 (lactam C=O), 157.76 (amide C=O), 139.10 (C=N), 140.03, 136.45, 135.19, 129.71, 129.15, 128.92, 128.72, 127.48, 127.32, 125.22, 125.02, 119.83
(12 aromatic carbons), 55.30 (CH), 40.18 (CH₂). MS: m/z = 402 [M⁺]. Anal for C₂₃H₁₉FN₄O₂ (402.43) (% Calcd./found): C, 68.65/68.81; H, 4.76/5.02; N, 13.92/14.02.

1-(4-Methylphenyl)-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (9a). Yield 67%, m.p. 170-172 °C. IR (KBr): cm⁻¹ 3375, 3246 (NH), 1675 (lactam C=O), 1651 (amide C=O), 1592 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.82 (s, 1H, PhNH), 7.58-7.14 (m, 9H, aromatic protons), 6.33 (s, 1H, NH), 4.24 (s, 2H, CH₂), 2.22 (s, 3H, CH₃); ¹³C NMR (CDCl₃): δ/ppm 160.33 (lactam C=O), 157.10 (amide C=O), 139.34 (C=N), 140.96, 136.92, 129.51, 129.19, 128.78, 127.31, 125.10, 119.87 (8 aromatic carbons), 43.77 (CH₂), 23.20 (CH₃). MS: m/z = 308 [M⁺]. Anal for C₁₇H₁₆N₄O₂ (308.34) (% Calcd./found): C, 66.22/66.28; H, 5.23/5.02; N, 18.17/18.00.

5-Methyl-1-(4-methylphenyl)-3-phenylaminocarbonyl-4,5-di-hydro-1,2,4-triazin-6-one (9b). Yield 63%, m.p. 140-142 °C. IR (KBr): cm⁻¹ 3355, 3230 (NH), 1678 (lactam C=O), 1654 (amide C=O), 1590 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.83 (s, 1H, PhNH), 8.96-7.14 (m, 9H, aromatic protons), 6.31 (s, 1H, NH), 4.37-4.32 (q, 1H, CH, J = 6.7 Hz), 2.26 (s, 3H, CH₃), 1.58-1.56 (d, 3H, CH₃, J = 6.7 Hz); ¹³C NMR (CDCl₃): δ/ppm 161.40 (lactam C=O), 157.67 (amide C=O), 139.31 (C=N), 140.94, 136.91, 129.48, 129.18, 128.73, 127.21, 125.14, 119.88 (8 aromatic carbons), 49.62 (CH), 23.28 (CH₃). MS: m/z = 322 [M⁺]. Anal for C₁₈H₁₈N₄O₂ (322.37) (% Calcd./found): C, 67.07/67.14; H, 5.63/5.43; N, 17.38/17.19.

1-(4-Methylphenyl)-5-phenylaminocarbonyl-4,5-di-hydro-1,2,4-triazin-6-one (9c). Yield 80%, m.p. 202-204 °C. IR (KBr): cm⁻¹ 3382, 3264 (NH), 1681 (lactam C=O), 1656 (amide C=O), 1604 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.80 (s, 1H, PhNH), 7.78-7.24 (m, 14H, aromatic protons), 6.72 (s, 1H, NH), 5.35 (s, 1H, CH), 2.30 (s, 3H, CH₃); ¹³C NMR (CDCl₃): δ/ppm 160.72 (lactam C=O), 157.70 (amide C=O), 139.00 (C=N), 141.08, 138.63, 138.10, 136.30, 132.55, 129.18, 129.11, 129.06, 128.69, 126.61, 125.08, 119.82 (12 aromatic carbons), 57.31 (CH), 23.30 (CH₃). MS: m/z = 384 [M⁺]. Anal for C₂₂H₂₀N₄O₂ (384.44) (% Calcd./found): C, 71.86/71.85; H, 5.24/5.19; N, 14.57/14.46.

5-Isopropyl-1-(4-methylphenyl)-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (9d). Yield 70%, m.p. 248-250 °C. IR (KBr): cm⁻¹ 3376, 3278 (NH), 1675 (lactam C=O), 1654 (amide C=O), 1596 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.83 (s, 1H, PhNH), 7.76-7.14 (m, 9H, aromatic protons), 6.35 (s, 1H, NH), 4.16-4.15 (d, 1H, CH, J = 6 Hz), 2.56-2.38 (m, 1H, CH), 2.25 (s, 3H, CH₃), 1.07-1.02 (d, 6H, 2CH₃, J = 6.8 Hz); ¹³C NMR (CDCl₃): δ/ppm 161.37 (lactam C=O), 157.37 (amide C=O), 138.70 (C=N), 140.69, 136.52, 129.17, 128.75, 127.25, 125.24, 125.03, 119.79, 8 (aromatic carbons), 59.11 (CH), 32.89 (CH), 23.27 (CH₃), 18.29, 16.66 (2 CH₃). MS: m/z = 350 [M⁺]. Anal for C₂₀H₂₂N₄O₂ (350.42) (% Calcd./found): C, 68.55/68.16; H, 6.33/6.61; N, 15.99/15.85.

5-Benzyl-1-(4-methylphenyl)-3-phenylaminocarbonyl-4,5-di-hydro-1,2,4-triazin-6-one (9e). Yield 61%, m.p. 258-260 °C. IR (KBr): cm⁻¹ 3368, 3257 (NH), 1677 (C=O lactam), 1653 (amide C=O), 1596 (C=N); ¹H NMR (CDCl₃): δ/ppm 8.63 (s, 1H, PhNH), 7.55-7.13 (m, 14H, aromatic protons), 6.25 (s, 1H, NH), 4.53-4.51 (t, 1H, CH, J = 6 Hz), 3.22-3.13 (d, 2H, CH₂, J = 8.4 Hz), 2.27 (s, 3H, CH₃); ¹³C NMR (CDCl₃): δ/ppm 160.78 (lactam C=O), 157.76 (amide C=O), 12 aromatic carbons), 55.30 (CH), 40.18 (CH₂).
139.10 (C=N), 140.03, 136.45, 135.19, 129.71, 129.15, 128.92, 128.72, 127.48, 127.32, 125.22, 125.02, 119.83 (12 aromatic carbons), 55.30 (CH), 40.18 (CH$_2$), 23.21 (CH$_3$). MS: $m/z = 398$ [M$^+$. Anal for C$_{24}$H$_{22}$N$_4$O$_2$ (398.47) (% Calcd./found): C, 72.34/72.73; H, 5.57/5.28; N, 14.06/13.94.

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**References and Notes**

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