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

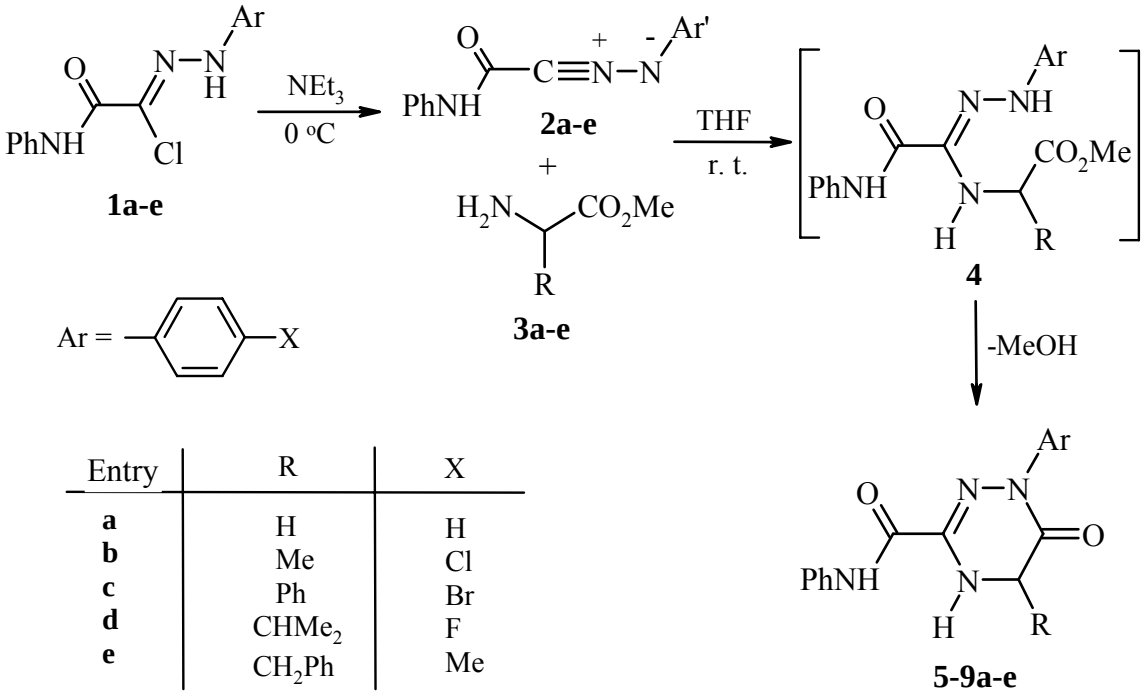
Introduction

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**.

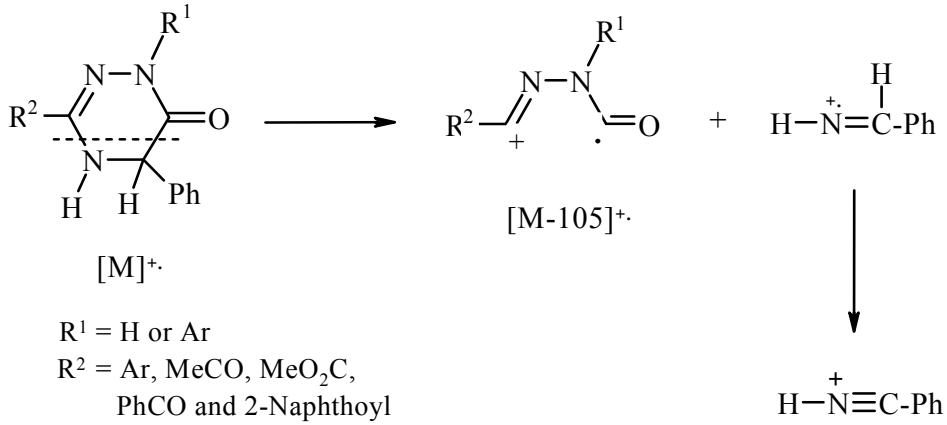
The assignment of structures **5-9a-e** is based on their analytical and spectroscopic data. Physical properties, molecular ion peaks and elemental analysis are presented in the Experimental Section. No investigations were carried out concerning optical purity and activity.

Spectrosopic 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 ^{13}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.[22,23] 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.



Scheme 2

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*.[24,25] 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_{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. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on Bruker AM 300 MHz and Jeol LA-300 instruments at 21 ^{o}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**[23,26,27] and α-amino ester hydrochlorides **3a-e**[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 °C. IR (KBr): cm^{-1} 3360, 3262 (NH), 1672 (lactam C=O), 1645 (amide C=O), 1590 (C=N); ^{1}H NMR ($CDCl_3$): δ/ppm 8.83 (s, 1H, PhNH), 7.58-7.14 (m, 10H, aromatic protons), 6.33 (s, 1H, NH), 4.24 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): 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 (CH_2). MS: *m/z* = 294 [M^+]. Anal for $C_{16}H_{14}N_4O_2$ (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 °C. IR (KBr): cm^{-1} 3355, 3253 (NH), 1676 (lactam C=O), 1647 (amide C=O), 1591 (C=N); ^{1}H NMR ($CDCl_3$): 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, CH_3, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$): 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 (CH_3). MS: *m/z* = 308 [M^+]. Anal for $C_{17}H_{16}N_4O_2$ (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 °C. IR (KBr): cm^{-1} 3360, 3267 (NH), 1672 (lactam C=O), 1648 (amide C=O), 1601 (C=N); ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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 $C_{22}H_{18}N_4O_2$ (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 °C. IR (KBr): cm^{-1} 3376, 3273 (NH), 1679 (lactam C=O), 1657 (amide C=O), 1600 (CN); ^{1}H NMR ($CDCl_3$): δ/ppm 8.83 (s, 1H, PhNH), 7.76-7.14 (m, 10H, aromatic protons), 6.35 (s, 1H, NH), 4.16-4.15 (d, 1H, CH, *J* = 6 Hz), 2.56-2.38 (m, 1H, CH), 1.07-1.0 (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* = 336 [M^+]. Anal for $C_{19}H_{20}N_4O_2$ (336.40) (% Calcd./found): C, 67.84/68.04; 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. 156-158 °C. IR (KBr): cm^{-1} 3355, 3273 (NH), 1676 (C=O lactam), 1650 (amide C=O), 1601 (C=N); ^{1}H NMR ($CDCl_3$): δ/ppm 8.63 (s, 1H, PhNH), 7.55-7.13 (m, 15H, 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 (CH_2). MS: *m/z* = 384 [M^+]. Anal for $C_{23}H_{20}N_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3387, 3291 (NH), 1682 (lactam C=O), 1655 (amide C=O), 1601 (C=N); ^1H NMR ($CDCl_3$): δ/ppm 8.80 (s, 1H, PhNH), 7.60-7.20 (m, 9H, aromatic protons), 6.39 (s, 1H, NH), 4.24 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ/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 $C_{16}H_{13}N_4O_2$ (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-di-hydro-1,2,4-triazin-6-one (6b). Yield 70%, m.p. 158-160 ^oC. IR (KBr): cm^{-1} 3358, 3264 (NH), 1683 (lactam C=O), 1660 (amide C=O), 1601 (C=N); ^1H NMR ($CDCl_3$): δ/ppm 8.80 (s, 1H, PhNH), 7.60-7.16 (m, 9H, aromatic protons), 6.40 (s, 1H, NH), 4.37-4.32 (q, 1H, CH, *J* = 6.7 Hz), 1.58-1.56 (d, 3H, CH_3, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ/ppm 160.55 (lactam C=O), 156.77 (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 $C_{17}H_{15}N_4O_2$ (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-di-hydro-1,2,4-triazin-6-one (6c). Yield 73%, m.p. 190-192 ^oC. IR (KBr): cm^{-1} 3375, 3273 (NH), 1679 (lactam C=O), 1662 (amide C=O), 1598 (C=N); ^1H NMR ($CDCl_3$): δ/ppm 8.83 (s, 1H, PhNH), 7.60-7.17 (m, 14H, aromatic protons), 6.81 (s, 1H, NH), 5.31 (s, 1H, CH); ^{13}C NMR ($CDCl_3$): δ/ppm 159.73 (lactam C=O), 156.73 (amide C=O), 139.00 (C=N), 138.63, 138.10, 136.30, 132.55, 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 $C_{22}H_{17}ClN_4O_2$ (404.86) (% Calcd./found): C, 65.27/65.54; H, 4.23/4.13; N, 13.84/13.69.

1-(4-Chlorophenyl)-5-isopropyl-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (6d). Yield 90%, m.p. 272-274 ^oC. IR (KBr): cm^{-1} 3366, 3263 (NH), 1675 (lactam C=O), 1662 (amide C=O), 1596 (C=N); ^1H NMR ($CDCl_3$): δ/ppm 8.81 (s, 1H, PhNH), 7.68-7.21 (m, 9H, aromatic protons), 6.35 (s, 1H, NH), 4.20-4.19 (d, 1H, CH, *J* = 6 Hz), 2.10-2.01 (m, 1H, CH), 1.09-1.07 (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* = 370/372 [M^+]. Anal for $C_{19}H_{19}ClN_4O_2$ (370.84) (% Calcd./found): C, 61.54/61.48; H, 5.16/5.12; N, 15.11/15.37.

5-Benzyl-1-(4-chlorophenyl)-3-phenylaminocarbonyl-4,5-dihydro-1,2,4-triazin-6-one (6e). Yield 90%, m.p. 270-272 ^oC. IR (KBr): cm^{-1} 3356, 3253 (NH), 1678 (C=O lactam), 1652 (amide C=O), 1597 (C=N); ^1H NMR ($CDCl_3$): δ/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), 3.24- 3.13 (d, 2H, CH_2, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ/ppm 160.75 (lactam C=O), 157.67 (amide C=O), 139.10 (C=N), 137.85, 136.82, 135.01, 130.34, 129.66, 129.17, 128.93, 128.77, 127.55, 126.28, 125.12, 119.82 (12

aromatic carbons), 55.26 (CH), 40.21 (CH_2). MS: *m/z* = 418/420 [M^+]. Anal for $C_{23}H_{19}ClN_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3349, 3236 (NH), 1685 (lactam C=O), 1654 (amide C=O), 1590 (C=N); ^1H 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 $C_{16}H_{13}BrN_4O_2$ (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-di-hydro-1,2,4-triazin-6-one (7b). Yield 67%, m.p. 170-172 ^oC. IR (KBr): cm^{-1} 3371, 3269 (NH), 1681 (lactam C=O), 1657 (amide C=O), 1598 (C=N); ^1H 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 $C_{17}H_{15}BrN_4O_2$ (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-di-hydro-1,2,4-triazin-6-one (7c). Yield 73%, m.p. 182-183 ^oC. IR (KBr): cm^{-1} 3366, 3271 (NH), 1677 (lactam C=O), 1658 (amide C=O), 1601 (C=N); ^1H 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 $C_{22}H_{17}BrN_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3349, 3264 (NH), 1679 (lactam C=O), 1661 (amide C=O), 1596 (C=N); ^1H 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 $C_{19}H_{19}BrN_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3361, 3253 (NH), 1678 (C=O lactam), 1653 (amide C=O), 1602 (C=N); ^1H NMR ($CDCl_3$): 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, 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 (CH_2). MS: *m/z* = 463/465 [M^+]. Anal for $C_{23}H_{19}BrN_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3348, 3240 (NH), 1674 (lactam C=O), 1655 (amide C=O), 1594 (C=N); ^1H NMR ($CDCl_3$): δ/ppm 9.99 (s, 1H, PhNH), 7.85-7.10 (m, 9H, aromatic protons), 6.12 (s, 1H, NH), 4.05 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): 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* = 312 [M^+]. Anal for $C_{16}H_{13}FN_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3366, 3244 (NH), 1672 (lactam C=O), 1657 (amide C=O), 1590 (C=N); ^1H NMR ($CDCl_3$): 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, CH_3, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$): 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 (CH_3). MS: *m/z* = 326 [M^+]. Anal for $C_{17}H_{15}FN_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3371, 3265 (NH), 1679 (lactam C=O), 1651 (amide C=O), 1596 (C=N); ^1H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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 $C_{22}H_{17}FN_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3382, 3252 (NH), 1683 (lactam C=O), 1654 (amide C=O), 1601 (C=N); ^1H NMR ($CDCl_3$): 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, $2CH_3$, *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* = 354 [M^+]. Anal for $C_{19}H_{19}FN_4O_2$ (354.39) (% Calcd./found): C, 64.40/64.77; H, 5.40/5.00; N, 15.81/15.85.

5-Benzyl-1-(4-fluorophenyl)-3-phenylaminocarbonyl-4,5-di-hydro-1,2,4-triazin-6-one (8e). Yield 70%, m.p. 206-208 ^oC. IR (KBr): cm^{-1} 3367, 3262 (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, 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 (CH_2). MS: *m/z* = 402 [M^+]. Anal for $C_{23}H_{19}FN_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3375, 3246 (NH), 1675 (lactam C=O), 1651 (amide C=O), 1592 (C=N); ^1H NMR ($CDCl_3$): δ/ppm 8.82 (s, 1H, PhNH), 7.58-7.14 (m, 9H, aromatic protons), 6.33 (s, 1H, NH), 4.24 (s, 2H, CH_2), 2.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 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 (CH_2), 23.20 (CH_3). MS: *m/z* = 308 [M^+]. Anal for $C_{17}H_{16}N_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3355, 3230 (NH), 1678 (lactam C=O), 1654 (amide C=O), 1590 (C=N); ^1H NMR ($CDCl_3$): 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, CH_3), 1.58-1.56 (d, 3H, CH_3, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$): 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 (CH_3), 19.67 (CH_3). MS: *m/z* = 322 [M^+]. Anal for $C_{18}H_{18}N_4O_2$ (322.37) (% Calcd./found): C, 67.07/67.14; H, 5.63/5.43; N, 17.38/17.19.

1-(4-Methylphenyl)-5-phenyl-3-phenylaminocarbonyl-4,5-di-hydro-1,2,4-triazin-6-one (9c). Yield 80%, m.p. 202-204 ^oC. IR (KBr): cm^{-1} 3382, 3264 (NH), 1681 (lactam C=O), 1656 (amide C=O), 1604 (C=N); ^1H NMR ($CDCl_3$): 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, CH_3); ^{13}C NMR ($CDCl_3$): 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 (CH_3). MS: *m/z* = 384 [M^+]. Anal for $C_{23}H_{20}N_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3376, 3278 (NH), 1675 (lactam C=O), 1654 (amide C=O), 1596 (C=N); ^1H NMR ($CDCl_3$): 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, CH_3), 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), 23.27 (CH_3), 18.29, 16.66 (2 CH_3). MS: *m/z* = 350 [M^+]. Anal for $C_{20}H_{22}N_4O_2$ (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 ^oC. IR (KBr): cm^{-1} 3368, 3257 (NH), 1677 (C=O lactam), 1653 (amide C=O), 1596 (C=N); ^1H NMR ($CDCl_3$): 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, CH_2, *J* = 8.4 Hz), 2.27 (s, 3H, CH3); ^{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 (CH_2), 23.21 (CH_3). MS: *m/z* = 398 [M^+]. Anal for $C_{24}H_{22}N_4O_2$ (398.47) (% Calcd./found): C, 72.34/72.73; H, 5.57/5.28; N, 14.06/13.94.

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