NOVEL 6-AZAPTERIDINES FROM BIFUNCTIONAL 1,2,4-TRIAZINES

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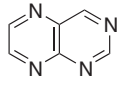
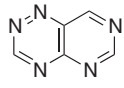
Dedicated to the memory of Professor Otakar Červinka.

The convergent synthesis of ethyl 5-chloro- and 5-amino-3-aryl-1,2,4-triazinecarboxylates **9a–9d** and **10a–10d** as well as of 5-amino-3-aryl-1,2,4-triazine-6-carboxamides **11a–11d** is described. Compounds **9**, **10** and **11** are powerful key compounds for cyclization reactions to the novel pyrimido[4,5-*e*][1,2,4]triazines **13d**, **14c**, **14d**, **15c** and **17a**, **17d**.
Keywords: Fused heterocycles; 1,2,4-Triazine; Pyrimido[4,5-*e*][1,2,4]triazine; 6-Azapteridine; Amidrazone; Amidine; 5-Chloro-1,2,4-triazine; 5-Amino-1,2,4-triazine.

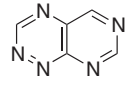
1,2,4-Triazines and pyrimido[1,2,4]triazines are considered as analogs of naturally occurring N-heterocycles, especially of pyrimidine bases, purines and pteridines. Several of them exhibit significant biological activities. Pharmacological and biochemical activities of *as*-triazines[1,2] and of azapteridines[3,4] are rather broad. Position of the introduced N atom leads to a classification into pyrimido[4,5-*e*][1,2,4]triazine (named also 6-azapteridines **2**) and pyrimido[5,4-*e*][1,2,4]triazines (7-azapteridines **3**), respectively. 6-Azapteridines have been much less investigated[3,4] in comparison with the 7-azapteridines.



pteridine (**1**)



6-azapteridine (**2**)

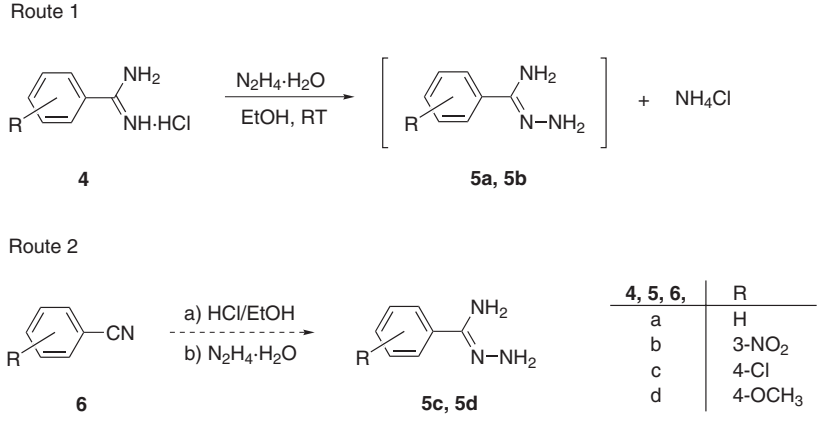


7-azapteridine (**3**)

Synthetic approaches towards 6-azapteridines can start either from pyrimidines, 1,2,4-triazines, or purines[3]. In this study, the annelation of pyrimidine ring to the 1,2,4-triazine ring is realized in two different ways: by [3+3] or [5+1] condensation. The 1,2,4-triazine derivatives required can be obtained by [4+2] atom combination, *i.e.* by condenzation reaction of sym-

metrically substituted 1,2-dicarbonyl compounds and hydrazidines, also known as amidrazones[1,2]. This method can be carried out smoothly, as no vigorous reaction conditions must be used, and the yields are rather high.

In order to obtain ethyl 5-oxo-4,5-dihydro-1,2,4-triazine-6-carboxylates **8a–8d**, amidrazones **5a**, **5b** are required (Scheme 1), the latter being very sensitive to light and oxygen, which cause fast dimerization reaction leading to red-violet tetrazines. Thus **5a**, **5b** must be prepared *in situ*. In any case, several side products are formed and the method requires difficult separation[5]. Newly substituted amidrazones **5c**, **5d** are obtained in two different ways (Scheme 1).



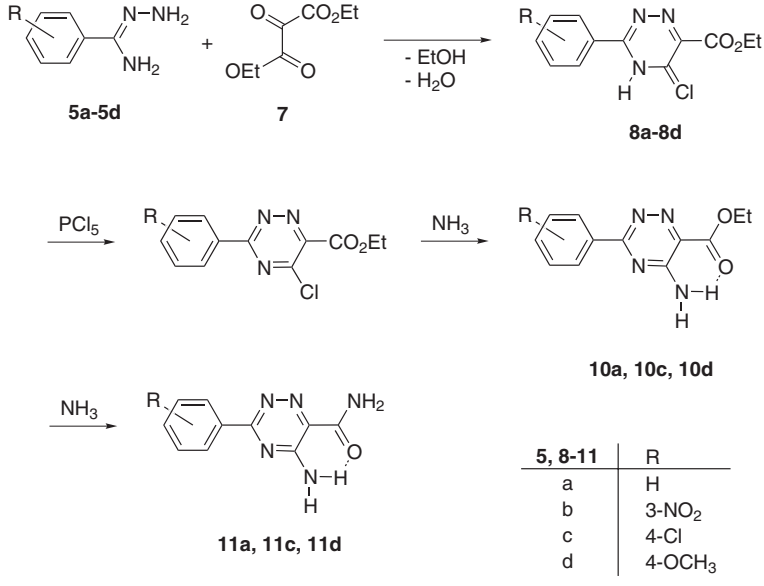
SCHEME 1

The amidrazones **5a**, **5b** generated from benzamidine hydrochloride **4** and hydrazine (Scheme 1, route 1) are not isolated but transformed *in situ* by reaction with diethyl oxomalonate (**7**) directly into the 1,2,4-triazin-5-ones **8a**, **8b**. This procedure looks quite simple, but offers only few advantages, as the reaction conditions (polar solvent, high temperature) favor the formation of side products, such as tetrazines and triazoles.

Synthesis of amidrazones **5a**, **5b** starting from benzonitriles proceeds *via* several steps[6,7] (Scheme 1, route 2) but proves to be much more effective as the yields are high and the products are easier to isolate.

The *in situ* prepared (Scheme 1, route 1) amidrazones **5a**, **5b** and diethyl oxomalonate (**7**) afford the 1,2,4-triazines **8a**, **8b** in ethanol as solvent, but together with several side products[5,6,8], while the other amidrazones **5c**, **5d** (Scheme 1, route 2) react with the diethyl oxomalonate (**7**) smoothly in propan-2-ol to afford 1,2,4-triazines[7] **8c**, **8d**.

The ethyl 5(4*H*)-oxo-1,2,4-triazine-6-carboxylates **8a–8d** are colorless solids with high melting points and high stability. From them are obtained the 5-chloro derivatives **9a–9d** with phosphorus pentachloride[8–10], but also accessible with the aid of phosphorus oxychloride[7,10] or thionyl chloride[10,11] (Scheme 2). The nucleophilicity of the chloro-substituted C-5 of the 1,2,4-triazine ring is similar to that of azalogous acid halides; thus, moisture hydrolyzes them back to the triazinones. However, nucleophiles such as ammonia or primary amines convert them smoothly to amino derivatives[8,10].



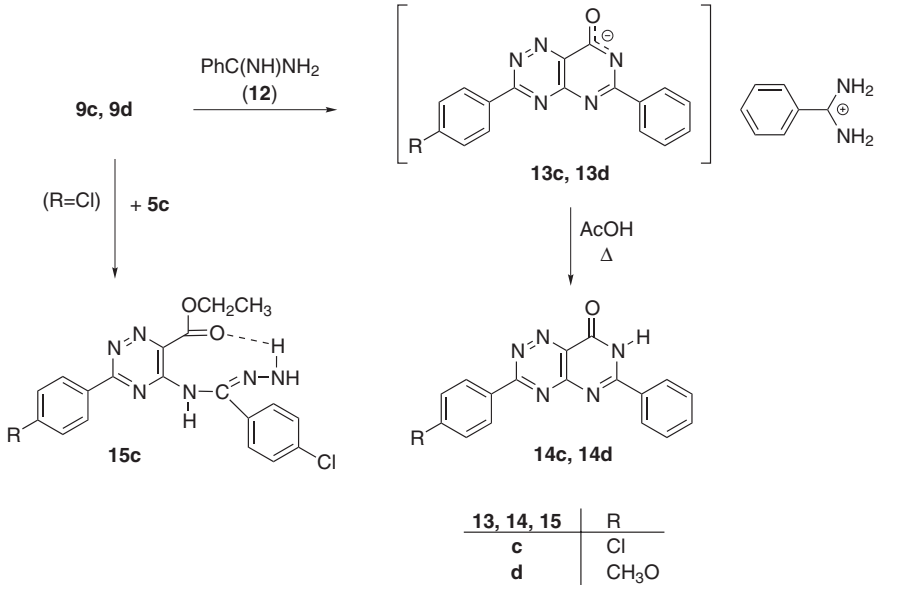
SCHEME 2

Synthesis of ethyl 5-amino-1,2,4-triazine-6-carboxylates **10a–10d** from chloro derivatives **9a–9d** must be carried out cautiously in oder to avoid side reactions; powdered triazines **10a–10d** are suspended in ethanol saturated with ammonia[7]. Monitoring the reaction time (optimum *ca* 30 min) is essential to avoid the attack of ammonia on the ester carbonyl leading to 5-amino-1,2,4-triazine-6-carboxamides **11a–11d**. Complete conversion to **11a–11d** at room temperature is achieved after 20 h (Scheme 2).

Compounds **9c**, **9d** are converted in a one-step reaction with benzamidine (**12**) to the 6-azapteridines **14c**, **14d** (Scheme 3). We were able to isolate and characterize an intermediate salt **13c**, which is converted to azapteridine **14c** in boiling acetic acid. By treatment of **9c** with benzamidrazone (**5c**) a nucleophilic displacement takes place on C-5 to afford compound **15c**, its constitution was proved by the ^{1}H NMR spectroscopic

data. The hydrazone protons form two singlets at 10.15 and 10.85 ppm, suggesting a stable intramolecular H-bridge.

In analogy to the reaction of **9c**, **9d** with benzamidine (**12**), the reaction of **9c** with benzamidrazone **5c** was expected to lead to a ring closure giving a 6- or 7-membered heterocycle. However, despite varying the molar ratio of the reactants, compound **15c** remained the only product observed (Scheme 3).

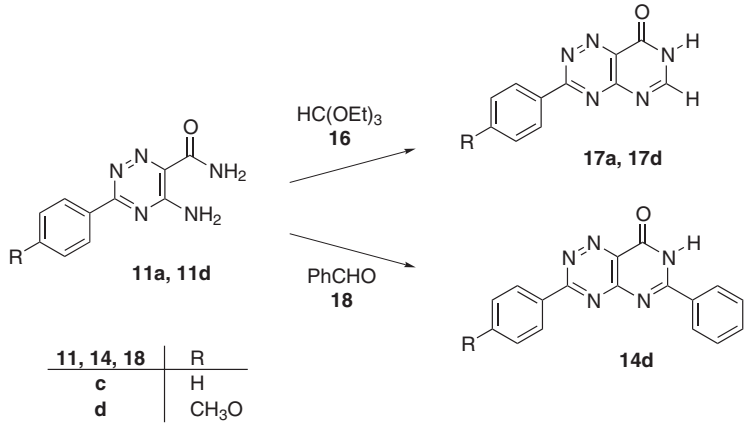


SCHEME 3

The 1,2,4-triazinecarboxamides **11a–11d** possess two nucleophilic centers in geometrically favorable positions, so their treatment with typical C-1 units should lead to fused pyrimidine systems. Pteridinone[12] and several pyrido[2,3-*d*]pyrimidin-4-ones[13] have been obtained accordingly. In our case, **11a**, **11d** and triethyl orthoformate (**16**) in the presence of acetic acid afforded 6-azapteridinones **17a**, **17d** (Scheme 4).

Another [5+1] condensation of **11** is represented by the reaction of **11d** with benzaldehyde (**18**) leading under dehydration conditions to azapteridine **14d** (Scheme 4).

In conclusion, we present a novel, versatile and simple approach to pyrimido[4,5-*e*][1,2,4]triazines. From the view of biological activities of similar compounds, the systems obtained might be considered as potential new structures deserving screening as drugs and/or crop protection agents.



SCHEME 4

EXPERIMENTAL

Melting points are not corrected, Leitz microscope. IR (KBr; ν, cm^{-1}): Perkin–Elmer FT-IR Paragon 500; UV: Beckman DU 640. MS: Kratos (A.E.I.) MS-30 and MS-50 (EI); Concept 1H (FAB, mNBA as matrix). ^1H, ^{13}C NMR (DMSO-d_6, TMS, δ 0, *J* in Hz): Bruker WM 300 (^1H: 300 MHz; ^{13}C: 75.0 MHz) and Bruker WM 400 (^1H: 400 MHz; ^{13}C: 100 MHz). Assignments were partly based on DEPT-spectra. Elemental analyses: Microanalytical Department of the Institute and Microanalytical Laboratory E. Pascher, Remagen. TLC: silica gel plates 60 F_{264} (Merck).

4-Chloro- and 4-Methoxybenzohydrazonamides **5c**, **5d**. General Procedure

Dry HCl stream was introduced into a solution of benzonitrile **6** (0.2 mol) in 200 ml of ethanol for 40 min under cooling with ice. The saturated ethanolic solution was kept at room temperature overnight, then the solvent was evaporated. The solid residue was suspended in a mixture of 5% aqueous KOH (250 ml) and diethyl ether (300 ml) and extracted, the aqueous layer being extracted with another 150 ml of diethyl ether. The combined organic layers were washed neutral with H_2O and dried over molecular sieve 4Å. After evaporation of the solvent to the half volume, a solution of 80% hydrazine monohydrate (12 ml; 0.2 mol) in ethanol (30 ml) was added and the mixture was stirred at room temperature until it became homogenous. After standing at 0 °C for 2 days, the solvent was removed *in vacuo*, and the residual product dissolved in 50 ml of diisopropyl ether. The crystals formed after cooling were filtered off and dried *in vacuo*.

4-Chlorobenzohydrazonamide[8] (**5c**). White flakes, yield 67%, m.p. 64–65 °C (i-Pr_2O). ^1H NMR ($CDCl_3$): 4.60 (s, 2 H, NH_2); 5.51 (s, 2 H, NNH_2); 7.27 (d, 2 H, *J* = 7, 3-H); 7.45 (d, 2 H, *J* = 7, 4-H). ^{13}C NMR ($CDCl_3$): 126.9 (C-3), 128.8 (C-4), 133.1 (C-5), 135.4 (C-2), 150.5 (C-1). IR (KBr): 3372.7, 3189.1 (NH_2), 1645.5 (C=N). MS, *m/z* (rel.%): 169.1 (63, M^+), 137.0 (100, $C_7H_4ClN^+$).

4-Methoxybenzohydrazonamide (**5d**). White flakes, yield 62%, m.p. 85–87 °C (i-Pr_2O). ^{1}H NMR ($CDCl_3$): 3.89 (s, 3 H, CH_3O); 4.95 (s, 2 H, NH_2); 5.68 (s, 2 H, NNH_2); 7.01 (d, 2 H, *J* = 7, 4-H); 7.77 (d, 2 H, *J* = 7, 3-H). ^{13}C NMR ($CDCl_3$): 54.9 (CH_3O), 113.2 (C-4), 126.3 (C-5), 128.1 (C-3), 145.5 (C-2), 159.1 (C-1). IR (KBr): 3394.5, 3269.1 (NH_2), 1639.8 (C=N). MS, *m/z* (rel.%): 165.2 (100, M^+).

Ethyl 5-Oxo-4,5-dihydro-1,2,4-triazine-6-carboxylates **8a**, **8b**. General Procedure

Benzamidine hydrochloride **4** (0.2 mol) was dissolved in 250 ml of ethanol and 80% hydrazine monohydrate ((12 ml, 0.2 mol) was added. The reaction mixture was stirred at ambient temperature, then the precipitated ammonium chloride was filtered off, as well as new precipitates which might form during filtration. Then, diethyl oxomalonate (**7**; 31 ml, 0.2 mol) was added under stirring and cooling with ice. The reaction mixture was stirred at room temperature for additional 16 h and then refluxed for 4 h. The mixture was cooled and the formed solid was filtered and crystallized from ethanol, the crystals were filtered and washed with diethyl ether.

Ethyl 5-oxo-3-phenyl-4,5-dihydro-1,2,4-triazine-6-carboxylate (**8a**). White crystals, yield 53%, m.p. 192–193 °C (EtOH); ref.[8] m.p. 197–199 °C.

Ethyl 3-(3-nitrophenyl)-5-oxo-4,5-dihydro-1,2,4-triazine-6-carboxylate (**8b**). Light yellow crystals, yield 49%, m.p. 182–183 °C (EtOH). For $C_{12}H_{10}N_4O_5$ (290.1) calculated: 49.66% C, 3.47% H, 19.30% N; found: 49.55% C, 3.48% H, 19.29% N. ^{1}H NMR (DMSO-d_6): 1.32 (t, 3 H, *J* = 7, CH_3); 4.36 (q, 2 H, *J* = 7, CH_2); 7.91 (t, 1 H, *J* = 8, 8-H); 8.49 (m, 2 H, 7-H, 9-H); 8.88 (s, 1 H, 5-H); 14.63 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 14.3 (CH_3), 62.3 (CH_2), 123.3 (C-8), 127.6 (C-7), 131.2 (C-9), 132.3 (C-5), 134.7 (C-4), 144.5 (C-6), 148.4 (C-3), 157.6 (C-1), 158.9 (C-2), 162.5 (COO). IR (KBr): 3455.8, (NH),1736.4 (CO, ester), 1623.4 (CO, lactam), 1533.3, 1349.5 (NO_2). UV (EtOH): 220 (4.29). MS, *m/z* (rel.%): 290.2 (21, M^+), 86.1 (100, $C_4H_5O^+$).

Ethyl 5-Oxo-4,5-dihydro-1,2,4-triazine-6-carboxylates **8c**, **8d**. General Procedure

Benzohydrazonamide **5a**, **5b** (0.1 mol) was dissolved in 200 ml of propan-2-ol and an equimolar amount of diethyl oxomalonate (**7**; 0.1 mmol, 15.5 ml) dissolved in the same alcohol was added under stirring and ice-cooling. Stirring was continued at room temperature for 18 h, the obtained white precipitate was filtered, crystallized from ethanol and washed with diethyl ether.

Ethyl 3-(4-chlorophenyl)-5-oxo-4,5-dihydro-1,2,4-triazine-6-carboxylate (**8c**). White crystals, yield 68%, m.p. 244–246 °C (EtOH); ref.[7] m.p. 244 °C.

Ethyl 3-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1,2,4-triazine-6-carboxylate (**8d**). White crystals, yield 66%, m.p. 216–218 °C (EtOH). For $C_{13}H_{13}N_3O_4$ (275.1) calculated: 56.72% C, 4.76% H, 15.27% N; found: 56.50% C, 4.73% H, 15.32% N. ^{1}H NMR (DMSO-d_6): 1.29 (t, 3 H, *J* = 7, CH_3); 3.86 (s, 3 H, CH_3O); 4.33 (q, 2 H, *J* = 7, CH_2); 7.15 (d, 2 H, *J* = 9, 6-H); 8.06 (d, 2 H, *J* = 9, 5-H); 14.25 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 13.8 (CH_3), 55.5 (CH_3O), 61.7 (CH_2), 114.4 (C-6), 121.6 (C-7), 129.8.2 (C-5), 142.8 (C-4), 158.0 (C-3), 158.8 (C-1), 162.2 (C-2), 163.0 (COO). IR (KBr): 3452.0 (NH), 1734.9 (CO, ester), 1609.4 (CO, lactam). UV (EtOH): 327 (3.97). MS, *m/z* (rel.%): 275.2 (35, M^+), 134.2 (100, $C_8H_8NO^+$).

Ethyl 5-Chloro-1,2,4-triazine-6-carboxylates **9a–9d**. General Procedure

1,2,4-Triazin-5-one **8a–8d** (0.1 mol) and PCl_5 (31.2 g, 0.15 mol) were suspended in 500 ml of absolute toluene and refluxed under argon for 1 h. After stirring at room temperature for 24 h, the dark yellow solution was washed three times with ice water and dried over anhydrous K_2CO_3. After evaporation, the obtained product was crystallized from diethyl ether.

Ethyl 5-chloro-3-phenyl-1,2,4-triazine-6-carboxylate (**9a**). Yellow crystals, yield 80%, m.p. 72–73 °C (Et_2O); ref.[8] m.p. 73–75 °C, ref.[10] 74–75 °C.

Ethyl 5-chloro-3-(4-chlorophenyl)-1,2,4-triazine-6-carboxylate (**9c**). Yellow crystals, yield 82%, m.p. 111–112 °C (Et_2O); ref.[10] m.p. 135 °C. For $C_{12}H_9Cl_2N_3O_2$ (297.0) calculated: 48.35% C, 3.04% H, 14.09% N; found: 48.06% C, 3.04% H, 13.82% N. ^{1}H NMR ($CDCl_3$): 1.41 (t, 3 H, J = 7, CH_3); 4.47 (q, 2 H, J = 7, CH_2); 7.48 (d, 2 H, J = 8, 5-H); 8.45 (d, 2 H, J = 8, 6-H). ^{13}C NMR ($CDCl_3$): 14.1 (CH_3), 63.4 (CH_2), 129.6 (C-5), 130.6 (C-6), 131.1 (C-7), 139.9 (C-4), 148.8 (C-3), 155.7 (C-1), 161.9 (C-2), 163.2 (COO). IR (KBr): 1731.3 (CO). UV ($CHCl_3$): 253 (4.17). MS, *m/z* (rel.%): 297.0 (17, M^+), 137.1 (100, $C_7H_4ClN^+$).

Ethyl 5-chloro-3-(4-methoxyphenyl)-1,2,4-triazine-6-carboxylate (**9d**). Yellow crystals, yield 68%, m.p. 89–90 °C (Et_2O). For $C_{13}H_{12}ClN_3O_3$ (293.1) calculated: 53.16% C, 4.12% H, 14.31% N; found: 48.06% C, 3.04% H, 13.82% N. ^{1}H NMR ($CDCl_3$): 1.44 (t, 3 H, J = 7, CH_3); 3.82 (s, 3 H, CH_3O); 4.58 (q, 2 H, J = 7, CH_2); 6.93 (d, 2 H, J = 9, 6-H); 8.41 (d, 2 H, J = 9, 5-H). ^{13}C NMR ($CDCl_3$): 14.1 (CH_3), 55.5 (CH_3O), 63.7 (CH_2), 114.2 (C-6), 126.6 (C-7), 130.8 (C-5), 140.4 (C-4), 160.7 (C-2), 162.2 (C-1), 163.2 (COO). IR (KBr): 1727.7 (CO). UV ($CHCl_3$): 316 (4.28). MS, *m/z* (rel.%): 293.1 (32, M^+), 133.1 (100, $C_8H_7NO^+$).

Ethyl 5-Amino-1,2,4-triazine-6-carboxylates **10a–10d**. General Procedure

Finely powdered 5-chloro-1,2,4-triazine **9a–9d** (25 mmol) was suspended portionwise in 100 ml of ethanol saturated with ammonia by ice cooling. Stirring of the solution was continued at room temperature for 30 min. After evaporation, the product was crystallized from ethanol.

Ethyl 5-amino-3-phenyl-1,2,4-triazine-6-carboxylate (**10a**). Yellow crystals, yield 90%, m.p. 177–178 °C (EtOH); ref.[8] m.p. 190–193 °C.

Ethyl 5-amino-3-(4-chlorophenyl)-1,2,4-triazine-6-carboxylate (**10c**). Yellow crystals, yield 93%, m.p. 245–247 °C (EtOH). For $C_{12}H_{11}ClN_4O_2$ (278.1) calculated: 51.72% C, 3.98% H, 20.10% N; found: 51.88% C, 4.05% H, 20.24% N. ^{1}H NMR (DMSO-d_6): 1.35 (t, 3 H, J = 7, CH_3); 4.40 (q, 2 H, J = 7, CH_2); 7.64 (d, 2 H, J = 8, 5-H); 7.85 (s, 1 H, NH); 8.36 (d, 2 H, J = 8, 6-H); 8.53 (s, 1 H, NH···O). ^{13}C NMR (DMSO-d_6): 14.3 (CH_3), 61.9 (CH_2), 129.6 (C-5), 130.2 (C-6), 133.1 (C-7), 133.8 (C-8), 137.4 (C-3), 155.4 (C-2), 161.5 (C-1), 164.9 (COO). IR (KBr): 3452.0, 3266.8 (NH_2), 1700.2 (CO). UV (EtOH): 332 (4.03). MS, *m/z* (rel.%): 278.1 (44, M^+), 68.1 (100, $C_7H_4ClN^+$).

Ethyl 5-amino-3-(4-methoxyphenyl)-1,2,4-triazine-6-carboxylate (**10d**). Yellow crystals, yield 92%, m.p. 224–225 °C (EtOH). For $C_{13}H_{14}N_4O_3$ (274.1) calculated: 56.93% C, 5.14% H, 20.43% N; found: 56.79% C, 5.44% H, 20.31% N. ^{1}H NMR (DMSO-d_6): 1.38 (t, 3 H, J = 7, CH_3); 3.83 (s, 3 H, CH_3O); 4.38 (q, 2 H, J = 7, CH_2); 7.01 (d, 2 H, J = 8, 6-H); 7.70 (s, 1 H, NH); 8.21 (s, 1 H, NH···O); 8.34 (d, 2 H, J = 9, 5-H). ^{13}C NMR (DMSO-d_6): 14.3 (CH_3), 55.6 (CH_3O), 61.8 (CH_2), 114.4 (C-6), 127.0 (C-7), 130.5 (C-5), 133.4 (C-4), 155.4 (C-2), 161.9 (C-3), 162.8 (C-1), 165.1 (COO). IR (KBr): 3443.7, 3279.1 (NH_2), 1696.8 (CO). UV (EtOH): 341 (4.32). MS, *m/z* (rel.%): 274.1 (33, M^+), 134.1 (100, $C_8H_7NO^+$).

5-Amino-1,2,4-triazine-6-carboxamides **11a**–**11d**. General Procedure

Finely powdered 5-chloro-1,2,4-triazine **9a**–**9d** (25 mmol) was suspended portionwise in 100 ml of ethanol and saturated with ammonia. The resulting solution was stirred at room temperature for 24 h. The residue after evaporation was crystallized from ethanol.

5-Amino-3-phenyl-1,2,4-triazine-6-carboxamide (**11a**). Yellow crystals, yield 79%, m.p. 271–272 °C (EtOH). For $C_{10}H_9N_5O$ (215.1) calculated: 55.81% C, 4.21% H, 32.54% N; found: 55.81% C, 4.08% H, 32.40% N. ^{1}H NMR (DMSO-d_6): 6.46 (m, 3 H, 6-H, 7-H); 6.79 (s, 1 H, NH); 7.17 (s, 1 H, NH···O); 7.30 (d, 2 H, J = 8, 5-H); 7.41 (s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6): 127.4 (C-6), 128.0 (C-5), 130.9 (C-7), 134.3 (C-4), 134.6 (C-2), 154.7 (C-3), 161.9 (C-1), 166.5 (CO). IR (KBr): 3462.2, 3402.0 (NH_2), 1672.5 (CO). UV (EtOH): 330 (3.98). MS, *m/z* (rel.%): 215.1 (72, M^+), 84.1 (100, $C_2H_2N_3O^+$).

5-Amino-3-chlorophenyl-1,2,4-triazine-6-carboxamide (**11c**). Yellow crystals, yield 77%, m.p. 297–298 °C (EtOH). For $C_{10}H_8ClN_5O$ (248.0) calculated: 48.11% C, 3.23% H, 28.05% N; found: 48.04% C, 3.41% H, 27.87% N. ^{1}H NMR (DMSO-d_6): 7.62 (d, 2 H, J = 8, 5-H); 7.87 (s, 1 H, NH); 8.34 (d, 3 H, J = 8, 6-H; s, 1 H, NH···O included); 8.49 (s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6): 129.2 (C-5), 130.0 (C-6), 134.3 (C-4), 135.4 (C-7), 136.8 (C-2), 155.4 (C-3), 161.8 (C-1), 167.2 (CO). IR (KBr): 3460.1, 3397.4 (NH_2), 1673.5 (CO). UV (EtOH): 332 (4.08). MS, *m/z* (rel.%): 248.0 (100, M^+).

5-Amino-3-methoxyphenyl-1,2,4-triazine-6-carboxamide (**11d**). Yellow crystals, yield 83%, m.p. 286–288 °C (EtOH). For $C_{11}H_{11}N_5O_2$ (245.1) calculated: 53.87% C, 4.52% H, 28.56% N; found: 53.67% C, 4.32% H, 28.60% N. ^{1}H NMR (DMSO-d_6): 3.84 (s, 3 H, CH_3O); 7.10 (d, 2 H, J = 9, 6-H); 7.86 (s, 1 H, NH); 8.26 (s, 1 H, NH···O); 8.32 (d, 2 H, J = 9, 5-H); 8.41 (s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6): 55.3 (s, 3 H, CH_3O), 114.0 (C-6), 114.4 (C-7), 127.2 (C-5), 129.6 (C-4), 134.3 (C-2), 154.9 (C-3), 162.0 (C-1), 166.9 (CO). IR (KBr): 3459.8, 3411.2 (NH_2), 1676.6 (CO). UV (EtOH): 337 (4.13). MS, *m/z* (rel.%): 245.1 (100, M^+).

3-(4-Chlorophenyl)-6-phenylpyrimido[4,5-*e*][1,2,4]triazin-8(7*H*)-one (**14c**)

5-Chloro-1,2,4-triazine **9c** (0.3 g, 1 mmol) was mixed under ice cooling with benzamidine (**12**; 0.6 g, 5 mmol). After heating at 120–130 °C for 1 h and cooling, the resulting precipitate was powdered and suspended in 20 ml of acetic acid. After refluxing for 30 min, the yellow precipitate was filtered off and crystallized from ethanol to provide 97% yield of yellow crystals, m.p. >400 °C (EtOH). For $C_{17}H_{10}ClN_5O$ (335.0) calculated: 60.81% C, 3.00% H, 20.86% N; found: 60.63% C, 2.98% H, 20.84% N. ^{1}H NMR (DMSO-d_6): 7.73 (m, 5 H, 11-, 12-, 13-H); 8.30 (d, 2 H, J = 8, 7-H); 8.60 (d, 2 H, J = 8, 8-H); 13.39 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 128.8 (C-13), 129.3 (C-12), 130.4 (C-11), 131.5 (C-10), 133.2 (C-8), 133.3 (C-6), 137.5 (C-9), 140.0 (C-3), 155.8 (C-5), 160.4 (C-4), 161.4 (C-2), 163.7 (C-1). IR (KBr): 3438.4 (NH), 1696.5 (CO). UV (EtOH): 348 (4.27). MS, *m/z* (rel.%): 335.0 (6, M^+), 104.1 ($C_7H_6N^+$).

Diamino(phenyl)methylium 3-(4-Methoxyphenyl)-6-phenylpyrimido[4,5-*e*][1,2,4]-triazin-8-olate (**13d**)

5-Chloro-1,2,4-triazine **9d** (0.6 g, 2 mmol) was mixed under ice cooling with benzamidine (**12**; 1.19 g, 10 mmol). Heating at 120–130 °C for 1 h, followed by powdering of the precipitate and twofold crystallization from ethanol provided 95% yield of yellow crystals, m.p. >355 °C (decomp.) (EtOH). For $C_{25}H_{21}N_7O_2$ (451.2) calculated: 65.21% C, 4.82% H, 21.29% N; found: 65.66% C, 4.54% H, 21.48% N. ^{1}H NMR (DMSO-d_6): 3.85 (s, 1 H, CH_3O); 7.15 (d,

2 H, *J* = 9, 8-H); 7.48 (d, 4 H, *J* = 7, 11-H, 12-H included); 7.62 (t, 1 H, *J* = 7, 13-H); 7.75 (t, 1 H, *J* = 7, 18-H); 7.85 (d, 2 H, *J* = 7, 17-H); 8.45 (d, 2 H, *J* = 7, 16-H); 8.55 (d, 2 H, *J* = 9, 7-H); 9.25 (s, 1 H, NH_2). ^{13}C NMR (DMSO-d_6): 55.3 (CH_3O), 114.2 (C-8), 127.9 (C-12), 128.0 (C-9), 128.1 (C-10), 128.3 (C-13), 128.6 (C-11), 128.9 (C-18), 129.8 (C-17), 130.6 (C-16), 133.6 (C-8), 138.7 (C-6), 138.9 (C-5), 156.8 (C-3), 161.8 (C-2), 162.7 (C-4), 165.6 (C-1), 169.2 (C-15), 170.2 (C-14). IR (KBr): 3325.5 (NH_2), 1684.3 (CO). UV (EtOH): 396 (4.21). MS, *m/z* (rel.%): 452.2 (51, M + H^+), 332.2 ($C_{18}H_{12}N_5O_2$ + H^+).

3-(4-Methoxyphenyl)-6-phenylpyrimido[4,5-*e*][1,2,4]triazin-8(7*H*)-one (**14d**)

Compound **13d** (0.45 mg, 1 mmol) was suspended in 20 ml of acetic acid and refluxed for 30 min. After cooling, the yellow precipitate was filtered off and crystallized from ethanol to give 95% yield of yellow crystals, m.p. 357–359 °C (EtOH). For $C_{18}H_{13}N_5O_2$ (331.1) calculated: 65.25% C, 3.65% H, 21.14% N; found: 64.96% C, 3.94% H, 21.04% N. ^1H NMR (DMSO-d_6): 3.93 (s, 3 H, CH_3O); 7.20 (d, 2 H, *J* = 9, 8-H); 7.60 (d, 2 H, *J* = 7, 11-H); 7.70 (t, 1 H, *J* = 7, 13-H); 8.28 (d, 2 H, *J* = 7, 12-H); 8.57 (d, 2 H, *J* = 9, 7-H); 13.31 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 55.5 (CH_3O), 114.6 (C-8), 126.6 (C-9), 128.7 (C-12), 128.8 (C-11), 130.6 (C-13), 131.0 (C-10), 131.7 (C-7), 132.0 (C-6), 133.1 (C-5), 139.2 (C-3), 161.2 (C-2), 162.8 (C-4), 164.4 (C-1). IR (KBr): 3432.2 (NH), 1703.0 (CO). UV (EtOH): 323 (4.09). MS, *m/z* (rel.%): 331.1 (6, M^+), 172.2 (100, $C_{10}H_6N_2O^+$).

Ethyl 5-(4-Chlorobenzohydrazonamido)-3-(4-chlorophenyl)-1,2,4-triazine-6-carboxylate (**15c**)

Finely powdered 5-chloro-1,2,4-triazine **9c** (0.3 g, 1 mmol) was mixed with amidrazone **5c** (0.34 g, 2 mmol) and the dry powder was heated at 60 °C for 1 h. The formed orange mass was suspended in 40 ml of dichloromethane and filtrated hot in order to remove excess amidrazone hydrochloride. The dichloromethane filtrate was evaporated to a third of its volume, the crude product was removed by filtration and washed with ethanol to give 74% yield of yellow crystals, m.p. 218–219 °C (CH_2Cl_2). For $C_{19}H_{16}Cl_2N_6O_2$ (430.1) calculated: 52.91% C, 3.74% H, 19.49% N; found: 52.59% C, 3.72% H, 19.49% N. ^1H NMR (DMSO-d_6): 1.36 (t, 3 H, *J* = 7, CH_3); 4.42 (q, 2 H, *J* = 7, CH_2); 6.90 (s, 1 H, NH); 7.47 (d, 2 H, *J* = 8, 12-H); 7.52 (d, 2 H, *J* = 8, 6-H); 7.83 (d, 2 H, *J* = 8, 13-H); 8.29 (d, 2 H, *J* = 8, 7-H); 10.15 (s, 1 H, 9-H); 10.85 (s, 1 H, 9′-H). ^{13}C NMR (DMSO-d_6): 14.4 (CH_3), 61.7 (CH_2), 128.5 (C-11), 128.6 (C-12), 129.3 (C-6), 129.9 (C-13), 130.3 (C-7), 132.9 (C-5), 134.3 (C-14), 135.1 (C-8), 136.7 (C-10), 140.4 (C-4), 150.4 (C-3), 160.3 (C-2), 165.5 (C-1). IR (KBr): 3435.6 (NH), 3267.0 (NH_2), 1674.1 (CO), 1636.5 (C=N). UV (CH_2Cl_2): 303 (4.45). MS, *m/z* (rel.%): 430.0 (100, M^+).

3-Phenylpyrimido[4,5-*e*][1,2,4]triazin-8(7*H*)-ones **17a**, **17d**. General Procedure

1,2,4-Triazine **11a**, **11d** was suspended in excess of triethyl orthoformate (**16**) and acetic anhydride was added. After refluxing for 2 h, the solution was evaporated and the formed solid was digested with chloroform. The crude product was filtered off and crystallized from ethanol.

3-Phenylpyrimido[4,5-e][1,2,4]triazin-8(7H)-one monohydrate (**17a**). Yellow-green crystals, yield 87%, m.p. >326 °C (decomp.) (EtOH). For $C_{11}H_7N_5O$ (225.1) calculated: 57.52% C, 3.29% H, 30.49% N; found: 57.78% C, 3.09% H, 30.20% N. ^1H NMR (DMSO-d_6): 7.65 (m, 3 H, 8-H, 9-H); 8.57 (m, 3 H, 7-H, 2-H included); 13.16 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6):

128.6 (C-8), 129.2 (C-9), 132.5 (C-7), 134.2 (C-6), 142.0 (C-5), 155.5 (C-2), 156.5 (C-3), 159.5 (C-4), 164.3 (C-1). IR (KBr): 3434.2 (NH), 1716.2 (CO), 1593.5 (C=N). UV (EtOH): 336 (4.07). MS, *m/z* (rel.%): 225.1 (6, M^+), 169.1 (100, $C_9H_5N_4^+$).

3-(4-Methoxyphenyl)pyrimido[4,5-e][1,2,4]triazin-8(7H)-one monohydrate (**17d**). Yellow-green crystals, yield 82%, m.p. >329 °C (decomp.) (EtOH). For $C_{12}H_9N_5O_2$ (255.1) calculated: 55.54% C, 3.81% H, 26.50% N; found: 54.66% C, 3.72% H, 26.20% N. ^{1}H NMR (DMSO-d_6): 3.90 (s, 3 H, CH_3); 7.19 (d, 2 H, J = 9, 8-H); 8.52 (s, 1 H, 2-H); 8.57 (d, 2 H, J = 9, 7-H); 13.01 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): 55.9 (CH_3), 115.2 (C-8), 126.9 (C-9), 131.1 (C-7), 141.0 (C-5), 155.6 (C-6), 156.5 (C-2), 159.7 (C-3), 163.4 (C-4), 164.7 (C-1). IR (KBr): 3438.0 (NH), 1718.9 (CO), 1602.9 (C=N). UV (EtOH): 335 (4.06). MS, *m/z* (rel.%): 255.1 (13, M^+), 199.1 (100, $C_{10}H_7N_4O^+$).

3-(4-Methoxyphenyl)-6-phenylpyrimido[4,5-*e*][1,2,4]triazin-8(7*H*)-one (**14d**)

Finely powdered 5-amino-1,2,4-triazine **11d** (245 mg, 1 mmol) was suspended in 5 ml of benzaldehyde (**18**) and the mixture refluxed for 1.5 h. After cooling to room temperature, the unreacted solid was filtered off. The filtrate was evaporated *in vacuo* and the residue was treated with 20 ml of hot propan-2-ol and active carbon. After hot filtration and evaporation of the solvent, the crude product was filtered off and crystallized three times from ethanol to give 12% yield of yellow crystals, m.p. 355 °C (EtOH). The identity of both products formed either by the reaction from **9d** *via* **13d** or from **11d** and **18**, respectively, was confirmed by TLC, IR and ^{1}H NMR spectra.

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