Communication

Mpelegeng Victoria Bvumbi*, Anza Imanuel Nemudzivhadi, Musiiwa Victoria Sengane and Simon Mnyakeni Moleele

Reactions of 3-amino-1,2,4-triazine with coupling reagents and electrophiles

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Abstract: Analogs of a new heterocyclic system were obtained from the reactions of 3-amino-1,2,4-triazine with coupling reagents such as boronic acids, and terminal alkynes in the presence of a palladium catalyst. Other reactions such as amination of the triazine at position 5, followed by electrophilic reactions with phenyl isocyanates and benzoyl chlorides, were performed to form new monoureido and benzoylated compounds.

Keywords: 3-amino-1,2,4-triazine, heterocyclic, electrophilic, monoureido, benzoylated

1 Introduction

Triazine is a heterocyclic ring analogous to the benzene ring but has three carbon atoms replaced by nitrogen atoms [1]. Due to its constituents of nitrogen on the ring, it is regarded as an important class of natural and non-natural products, many of which exhibit pharmacological activities [2]. Three known classes of triazines are 1,2,3-triazine, 1,3,5- or *s*-triazine, and 1,2,4- or *as*-triazine. 1,2,4-Triazine and its derivatives occupy a crucial position in medicinal chemistry because of their high potential for pharmacological activities. The activities include among others anti-cancer [3–5], analgesic and anti-inflammatory [6–8], anti-HIV [9,10], anti-microbial [11–13], and antimalarial [14–18]. Since the reported studies of March et al. [15] and Rees et al. [16] on 3,5-diamino-1,2,4-analogs in the 1970s, not much research has been done directly on this moiety. Their compounds were tested against *Plasmodium berghei* in mice and *Plasmodium gallinaceum* in chicks. In the former tests, more compounds showed activity, whereas, in the latter, halogen-like substituents in the fourth position of the aromatic group were more active. Hence, this work explored the modification and optimization of different electrophiles and carbon–carbon coupling on mono- and di-amino-1,2,4-triazine (Figure 1).

2 Results and discussion

Target mono- and di-amino-1,2,4-triazine analogs were synthesized following different reaction steps outlined in Schemes 1–3. The route employed to synthesize substituted ethynyl-1,2,4-triazin-3-amine involved the Sonogashira coupling reaction of 3-amino-6-bromo-1,2,4-triazine with terminal (phenyl and alkyl) alkynes in the presence of a palladium catalyst, copper(I) iodide, a base, and a solvent, **5a–d**. The reactions gave fair to good yields of 58–87%. The amine group was introduced at the C-5 position following a Chichibabin reaction in the presence of aqueous ammonia and oxidizing potassium permanganate to give compound **6**. Suzuki-Miyaura cross-coupling reactions yielded compounds **7a–d** in moderate yields, Scheme 1 [16]. The reaction of 3,5-diamino-1,2,4-triazine with various aromatic isocyanates occurred via the conventional addition to the amino group to give the corresponding arylureido analogs. When triethylamine, which is known to behave catalytically in the reaction between amines and isocyanates, was used, very small to no products were obtained. However, in these reactions, dimethoxyethane (DME) was used as a solvent and improved the yields of the products (30–62%). In addition, temperature conditions played a significant role in these electrophilic reactions. For instance, under reflux, mixtures of monureide were isolated by column chromatography. March et al. in their sets of experiments (which were substituted at position 6), could not determine

* **Corresponding author: Mpelegeng Victoria Bvumbi,** Department of Chemistry, Faculty of Science, Engineering and Agriculture, University of Venda, Private Bag X5050, Thohoyandou 0950, South Africa, e-mail: mpelegeng.bvumbi@univen.ac.za
Anza Imanuel Nemudzivhadi, Musiiwa Victoria Sengane, Simon Mnyakeni Moleele: Department of Chemistry, Faculty of Science, Engineering and Agriculture, University of Venda, Private Bag X5050, Thohoyandou 0950, South Africa

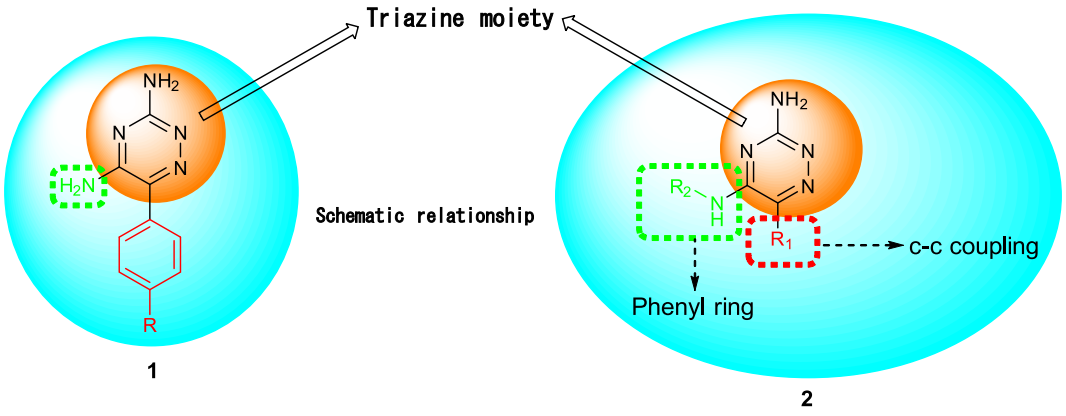
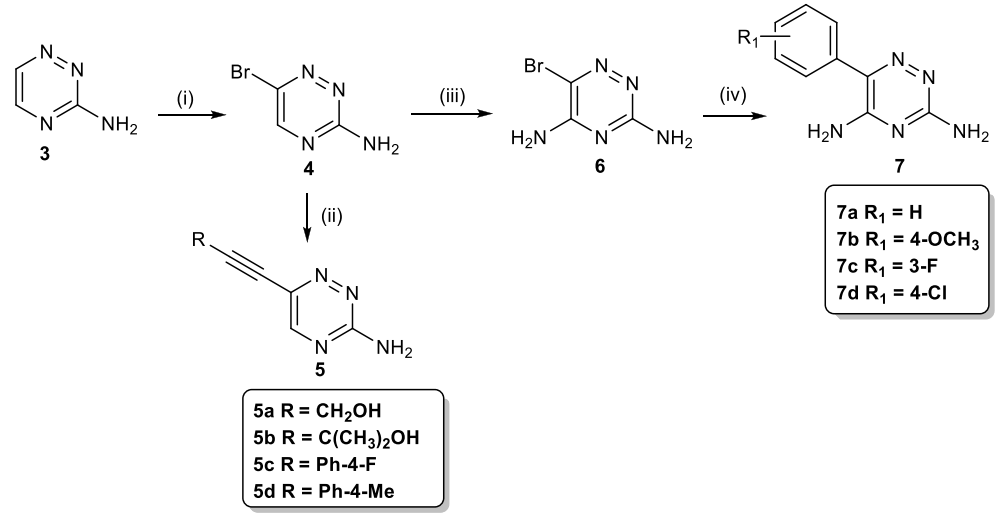


Figure 1: Schematic representation of the reported (**1**) and proposed 3-amino-1,2,4-triazine analogs (**2**).



Scheme 1: Reactions of 3-amino-1,2,4-triazine with coupling reagents: (i) Br_2, MeOH: H_2O, RT, 6 h, (ii) $Pd(PPh_3)_4$, terminal alkynes, Cu(I) iodide, Et_3N, tetrahydrofuran (THF), 65°C, 18 h, (iii) NH_3(aq), $KMnO_4$, RT, 16 h and (iv) $Pd(PPh_3)_4$, boronic acids, Na_2CO_3, EtOH, H_2O, 1,4-dioxane, reflux, 16 h.

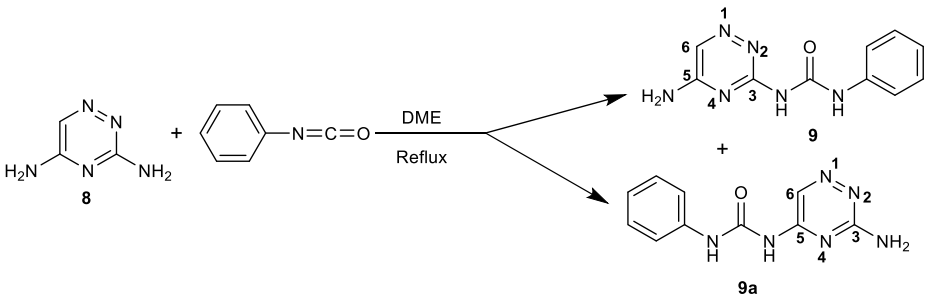
whether the reaction of 3,5-diamino-1,2,4-triazine with isocyanates occurred at 3 or 5 positions based on ^{1}H NMR and IR. We, however, were able to distinguish the two using the same NMR analytical tool.

Products **9** and **9a** were obtained in 10 and 30% yields, respectively. Their ^{1}H NMR spectra showed signals of both NH protons at 9.72 and 11.57 ppm for **9** and 9.99 and 10.43 ppm for **9a**, respectively, Scheme 2. Also, their H-6 were more shielded when compared to 8 by 0.29 and 0.72 ppm. The chemical shift changes of H-6 in 3,5-diamino-1,2,4-triazines when isocyanates are added differentiated the positions of the ring where the reactions took place (at C-3, NH_2 for **9** and C-5, NH_2 for **9a**).

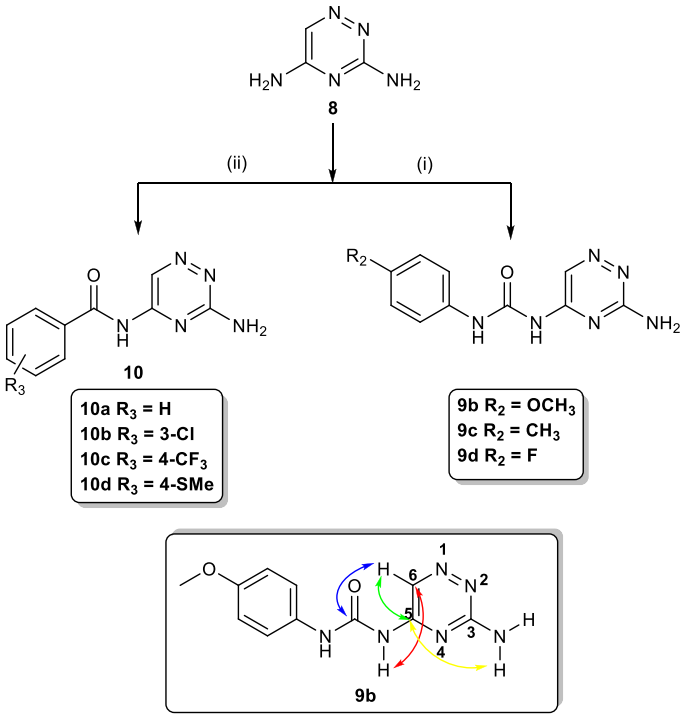
Stable monoarylureido analogs were obtained when reactions took place at room temperatures rather than at higher temperatures, **9b–d** with moderate yields of 30–62%. HMBC NMR spectroscopy correlations performed on **9b** (depicted in Scheme 3) further confirmed the position of the reaction (which is at the NH_2 of the C-5 position). The C–H at position 6 was the reference point for confirmation of the compound. Notable and robust correlations were observed between C-6 and the NH (next to the C-5, 3-bonds away) and between H-6 and C-5 (2-bonds away). In addition, a correlation between proton H-6 of the ring with CO in four bonds away further confirmed urea's presence in position 5 of the ring.

Surprisingly, a correlation (4-bonds away) was observed between an amine proton (C-3–NH_2) and C-5.

The triazine ring seems to have a strong electron-withdrawing effect that causes the deactivation of the 3-amino group towards an electrophilic attack. This was observed in the electrophilic reactions with benzoyl chlorides that had to be electrophile "strong" enough to be attacked by such an amino group and form the mono-



Scheme 2: Reaction of 3,5-diamino-1,2,4-triazine with phenyl isocyanate: DME, phenyl isocyanate, reflux, 16 h.



Scheme 3: Electrophilic addition reactions and selected HMBC correlations of **9b**: (i) DME, phenyl isocyanate, RT, 16 h and (ii) DCM or $CHCl_3$, TEA, benzoyl chlorides, RT/reflux, 18 h.

benzoylated products. Irrespective of the temperatures applied, reactions with benzoyl chlorides occurred at the amine position 5 of the triazine ring, **10a–d**, and gave moderate yields of 50–66%, Scheme 3. The reactions were carried out in the presence of triethylamine for 18 h at room temperatures or under reflux depending on the benzoyl chloride used.

3 Conclusion

In summary, the electrophilic syntheses of arylureido and benzoylated analogs were carried out in a base's absence and presence, respectively. Furthermore, the temperature dependence in both the reactions showed how different the electrophiles behave on the 3-amino-1,2,4-triazine ring moiety. It afforded synthetic means to show which amine position on the ring is more favorable than the other. The Suzuki-Miyaura and Sonogashira cross-coupling reactions demonstrated how well they behaved on both mono- and di-amino-1,2,4-triazine.

4 Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometers at 20°C in dimethylsulfoxide (DMSO-d_6) in the presence of tetramethylsilane as internal standard.

The Synapt G1 high definition mass spectrometer, equipped with electrospray ionization (ESI) source, was used to analyze the compounds by acquiring centroid data in both positive and negative ionization modes. The conditions for the MS detector were set as: capillary voltage of 2.5 kV, source temperature of 120°C, sampling cone voltage of 30 V, cone gas flow of 50.0 (L/h), extraction cone of 4.0 V, desolvation gas flow of 550 (L/h), *m*/*z* range of 100–1,000, scan time of 0.2 s, and an interscan delay of 0.02 s. Leucine encephalin $[M + H]^+$ = 552.766 and $[M - H]^-$ = 554.2615 was done to ensure that high mass was used as a reference calibrant to ensure high mass accuracy (2–5 mDA). The MS analyses were set to result in both unfragmented and fragmented experiments through collision-induced dissociation (MSE) achieved by alternating the collision energy from 10 to 50 eV. Due to better ionization in ESI negative mode, negative ionization data were processed in most of the compounds while a few positive ionization data were also processed. All the melting points were determined on a Buchi melting point B-540 apparatus. Qualitative analysis of the reaction mixtures was carried out using thin-layer chromatography on silica gel 60 F245, silufol UV-245, and alugram N/UN245 plates, eluting with methanol and dichloromethane.

4.1 General synthesis of compounds 5a–d, 9, 9a–d, and 10a–d

Compounds **5a–d** were obtained from the reactions of **4** with terminal alkynes in dry THF (25 mL) in the presence of copper(I) iodide, palladium (0) catalyst, and base, triethylamine. The reaction mixture was heated at 65°C, stirred, and refluxed for 18 h under a nitrogen atmosphere. The reaction was worked up by liquid–liquid extraction using ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered, excess solvent removed under reduced pressure, and the products were isolated by column chromatography on silica gel eluting with ethyl acetate/hexane (5:95–30:70) or methanol/dichloromethane (5:95).

Chichibabin amination of compound **6** was obtained from 6-bromo-1,2,4-triazin-3-amine **4** (12.31 mmol) in aqueous ammonium. The reaction mixture was stirred vigorously for 20–30 min before adding potassium permanganate (18.50 mmol) portion-wise into the reaction mixture. The resultant dark brown mixture was continued to stir for 24 h at room temperature. The excess solvent was removed under reduced pressure. The resulting dark brown crude solid was extracted with hot isopropanol, filtered, and the excess solvent was removed under reduced pressure, and soft lime solid (42%) was obtained as the required compound [19].

To the substrate (**8**) dimethoxyethane (DME) (10 mmol) was added followed by phenyl isocyanates. The resultant mixture was refluxed for 16 h over which time a precipitate was formed. The precipitate was collected by filtrate and the crude solid was purified by column chromatography, eluting with methanol and dichloromethane to give compounds **9** and **9a**. When the same reactions were done at room temperatures, compounds **9b–d** were obtained. When a solution of **8** in dichloromethane or chloroform reacted in the presence of triethylamine and benzoyl chlorides, at either room temperatures or refluxed, the products, **10a–d** were isolated by column chromatography on silica gel and eluted with methanol and dichloromethane 2:98–10:90.

4.1.1 3-(3-Amino-1,2,4-triazin-6-yl)prop-2-yn-1-ol (5a)

The compound was obtained from **4**, alkyne (propargyl alcohol), in 69% as a pale-yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.61 (br s, 2H), 5.47 (br t, 1H, J = 3.6 Hz), 4.34 (d, 2H, J = 3.9 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.8, 152.4, 136.5, 94.0, 78.9, 49.4. m.p. 195–197°C. HRMS (ESI-TOF+): *m*/*z* calcd for $C_6H_6N_4O$: 149.0501, found: 149.0092 (MH–). **IR (cm^{-1})**: 3299.6 (O–H stretch), 3178.4 (N–H), 2917.6 (C–H), 2105.5 (C ≡ C), 1645.1 (C═N).

4.1.2 4-(3-Amino-1,2,4-triazin-6-yl)-2-methylbut-3-yn-2-ol (5b)

The compound was obtained from **4**, alkyne (2-methylbut-3-yn-2-ol), in 58% as a pale-yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.59 (br s, 2H), 5.62 (br s, 1H), 1.47 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.7, 152.2, 136.5, 99.9, 75.8, 63.7, 31.3. m.p. 187–190.2°C. HRMS (ESI-TOF+): *m*/*z* calcd for $C_8H_{10}N_4O$: 179.0924, found: 179.0692 (MH+). **IR (cm^{-1})**: 3319.8 (O–H stretch), 3174.9 (N–H stretch), 3027.3 (C–H), 1644.9 (C═N), 1509.4 (C═C).

4.1.3 6-((4-Fluorophenyl)ethynyl)-1,2,4-triazin-3-amine (5c)

The product was obtained from **4**, alkyne (1-ethynyl-4-fluorobenzene), in 87% as orange solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.73 (br s, 2H) 7.68–7.60 (m, 2H), 7.29 (t, 2H, J = 8.7 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.4 (d, J_{C-F} = 248.6 Hz), 160.7, 152.5, 136.4, 133.8 (d, J_{C-F} = 8.7 Hz), 117.9 (d, J_{C-F} = 3.3 Hz), 116.2 (d, J_{C-F} = 22.3 Hz), 92.0, 84.2. m.p. 205–207.1°C. HRMS (ESI-TOF+): *m*/*z* calcd for $C_{11}H_7FN_4$: 212.0731, found: 212.1624 (MH2–). **IR (cm^{-1})**: 3487.5 (N–H), 2955.7 (C–H), 2852.1 (C ≡ C), 1624.6 (C═H), 1026.1 (C–F).

4.1.4 6-(*p*-Tolylethynyl)-1,2,4-triazin-3-amine (5d)

The product was obtained from **4**, alkyne (4-ethynyltoluene) in 67% as pale-yellow; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.70 (br s, 2H), 7.48 (d, 2H, J = 7.8 Hz,), 7.26 (d, 2H, J = 7.8 Hz), 2.34 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.7, 152.5, 139.3, 136.6, 131.3, 129.5, 118.4, 93.3, 83.9, 21.1. m.p. 221–223°C. HRMS (ESI-TOF+): m/z calcd for $C_{12}H_{10}N_4$: 211.0943, found: 211.0935 (MH+). **IR (cm^{-1})**: 3320.21 (N–H, sharp peak), 3138.11 (C–N, broad peak), 2918.61 (C–H stretch), 2079.6 (C ≡ C), 1651.3 (C═N, sharp peak), 1539.2 (C═C on benzene ring).

4.1.5 1-(5-Amino-1,2,4-triazin-3-yl)-3-phenylurea (9)

The compound was obtained from **8** in 10% as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.56 (s, 1H), 9.72 (s, 1H), 8.19 (s, 1H), 7.92 (br s, 2H), 7.60 (d, 3H, J = 7.8 Hz), 7.32 (t, 2H, J = 7.8 Hz), 7.05 (t, 1H, J = 7.3 Hz).

4.1.6 1-(3-amino-1,2,4-triazin-5-yl)-3-phenylurea (9a)

The compound was obtained from **8** in 30% as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 9.99 (s, 1H), 8.62 (s, 1H), 7.62 (d, 2H, J = 7.8 Hz), 7.33 (t, 2H, J = 7.9 Hz), 7.14 (s, 2H), 7.07 (t, 1H, J = 7.4 Hz). ^{13}C NMR (101 MHz, DMSO) δ 161.3, 152.1, 151.8, 138.7, 131.7, 129.3, 123.8, 119.9, m.p. 214–217°C. HRMS (ESI-TOF+): m/z calcd for $C_{10}H_{10}N_6O$: 231.0921, found: 231.0324 (MH+). **IR (cm^{-1})**: 3190.81 (N–H), 3038.16 (C–H), 1633.26 (C═N), 1530.88 (C═O).

4.1.7 1-(3-Amino-1,2,4-triazin-5-yl)-3-(4-methoxyphenyl)urea (9b)

The compound was obtained from **8** in 52% as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 10.26 (s, 1H), 9.93 (s, 1H), 8.52 (s, 1H), 7.53 (d, 2H, J = 9.0 Hz), 7.14 (s, 2H), 6.90 (d, 2H, J = 9.0 Hz), 3.73 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 160.7, 155.5, 151.6, 151.4, 131.1, 121.4, 113.9, 55.2, m.p. 235–237°C. HRMS (ESI-TOF+): m/z calcd for $C_{11}H_{12}N_6O_2$: 261.1056, found: 261.1801 (MH+). **IR (cm^{-1})**: 3494.46 (N–H), 3084.40 (C–H), 1651.40 (C═O), 1612.59 (C═N), 1519.76 (C–O).

4.1.8 1-(3-Amino-1,2,4-triazin-5-yl)-3-(p-tolyl)urea (9c)

The compound was obtained from **8** in 40% as a faint-yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 10.32 (s, 1H), 9.97 (s, 1H), 8.54 (s, 1H), 7.50 (d, 2H, J = 8.4 Hz), 7.25–6.99 (m, 2H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 160.9, 151.8, 151.5, 135.7, 132.6, 131.4, 129.4, 119.8, 20.6, m.p. 202–205°C. HRMS (ESI-TOF+): m/z calcd for $C_{11}H_{12}N_6O$: 243.1107, found: 243.1688 (MH–). **IR (cm^{-1})**: 3290.91 (N–H), 2121.0 (N–H), 3131.0 (C–H), 1651.3 (C═O).

4.1.9 1-(3-Amino-1,2,4-triazin-5-yl)-3-(4-fluorophenyl) urea (9d)

The compound was obtained from **8** in 62% as a bright-yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 10.48 (s, 1H), 10.04 (s, 1H), 8.52 (s, 1H), 7.88–7.38 (m, 2H), 7.33–7.02 (m, 4H). ^{13}C NMR (101 MHz, DMSO) ^{13}C NMR (101 MHz, DMSO) δ 161.8 (d, J = 224.8 Hz), 152.0, 151.6, 134.5 (d, J = 2.6 Hz), 131.2, 122.0, 121.6 (d, J = 7.9 Hz), 115.4 (d, J = 22.2 Hz), m.p. 246–248°C. HRMS (ESI-TOF+): m/z calcd for $C_{10}H_9FN_6O$: 247.0822, found: 247.0469 (MH–). **IR (cm^{-1})**: 3132.2 (N–H), 2918.4 (N–H), 1651.3 (C═O), 1469 (C–F).

4.1.10 *N*-(3-Amino-1,2,4-triazin-5-yl)benzamide (10a)

The compound was obtained from **8** in 50% as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.34 (s, 1H), 8.08–7.87 (m, 2H), 7.70–7.59 (m, 1H), 7.56–7.45 (m, 2H), 7.00 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 167.1, 162.4, 152.4, 133.1, 132.8, 130.8, 129.3, 128.5, m.p. 197–199°C. HRMS (ESI-TOF+): m/z calcd for $C_{10}H_9N_5O$: 216.0800, found: 216.1576 (MH+). **IR (cm^{-1})**: 3313.1 (N–H), 2920.3 (C–H), 1703.3 (C═O), 1663.3 (C═N).

4.1.11 *N*-(3-Amino-1,2,4-triazin-5-yl)-3-chlorobenzamide (10b)

The compound was obtained from **8** in 66% as a cream white solid. ^{1}H NMR (400 MHz, DMSO) δ 11.20 (s, 1H), 9.31 (s, 1H), 8.04 (s, 1H), 7.93 (d, 1H, J = 7.7 Hz), 7.70 (d, 1H, J = 8.0 Hz), 7.56 (t, 1H, J = 7.9 Hz), 7.01 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 165.8, 162.5, 152.2, 135.1, 133.2, 132.7, 132.4, 130.4, 128.3, 127.2, m.p. 216–218°C. HRMS (ESI-TOF+): m/z calcd for $C_{10}H_8ClN_5O$: 247.0468, found: 247.0475(MH–). **IR (cm^{-1})**: 3291.9 (N–H), 2920.5 (C–H), 1780.4 (C═O), 1680.6 (C═N), 709.2 (C–Cl).

4.1.12 *N*-(3-Amino-1,2,4-triazin-5-yl)-4-(trifluoromethyl) benzamide (10c)

The compound was obtained from **8** in 58% as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.35 (s, 1H),

9.35 (s, 1H), 8.16 (dd, 2H, J = 12.1, 8.3 Hz), 7.99–7.77 (m, 2H), 7.05 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 166.2, 162.5, 152.1, 136.9, 132.7, 130.1, 129.4, 125.6 (d, J = 3.8 Hz), 125.4 (d, J = 3.7 Hz), 122.5, m.p. 257–259°C. HRMS (ESI-TOF+): m/z calcd for $C_{11}H_8F_3N_5O$: 282.0741, found: 282.2771 (MH−). **IR (cm^{-1})**: 3387.4 (N–H), 3274.3 (C–H), 1692.3 (C═O), 1566.9 (C═N), 1112.5 (CF_3).

4.1.13 *N*-(3-Amino-1,2,4-triazin-5-yl)-4-(methylthio) benzamide (10d)

The compound was obtained from **8** in 62% as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 9.34 (s, 1H), 7.96 (d, 2H, J = 8.4 Hz), 7.37 (d, 2H, J = 8.4 Hz), 6.96 (br s, 2H), 3.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.3, 162.5, 152.3, 144.9, 132.8, 128.9, 124.7, 13.9, m.p. 200–202°C. HRMS (ESI-TOF+): m/z calcd for $C_{11}H_{11}N_5OS$: 261.0736, found: 261.1788 (MH). **IR (cm^{-1})**: 3083.2 (N–H), 2831.6 (C–H), 1792.0 (C═O), 1668.9 (C═N), 1327.61 (C–S).

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Conflict of interest: Authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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