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# Copper-mediated ligand-free Ullmann reaction approach to substituted *s*-triazines: rationale, synthesis, and biological evaluation

**Abstract:** Two series of *s*-triazine derivatives were synthesized by copper-catalyzed Ullmann reaction. Facile route was adopted to achieve amination of *s*-triazines for the first time. The C-N coupling reactions were conducted in water under ligand-free and oxygen-free conditions. The synthesized compounds were screened for their *in vitro* antibacterial and antifungal activity. Compounds were further subjected to *in vitro* antitubercular screening against the H37Rv strain. Compared with standard drugs, compound **5b** was found to be the most active antimicrobial and antitubercular agent that inhibits *Staphylococcus aureu*s and H37Rv strain with minimum inhibitory concentration of 1.56 and 6.25 μg/mL, respectively.

**Keywords:** antimicrobial; antitubercular; copper powder; *s*-triazine amination; Ullmann C-N coupling.

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## Introduction

During the past few decades, the growing human population has been affected by significant increase in the frequency of severe infectious diseases because of the increasing number of multi-drug-resistant (MDR) microbial pathogens [1–3]. These organisms multiply with the ability to resist the available antimicrobial drugs, and this uncontrolled rise in resistant pathogens may affect the immunocompromised individuals, patients with malignancies, and transplant recipients [4, 5]. In particular, tuberculosis (TB) has emerged as one of the most complicated infectious diseases worldwide. MDR and extensively drug-resistant TB are major two types of TB caused by some mycobacteria of the *Mycobacterium tuberculosis* complex that commonly affect the lungs [6–8]. According to World Health Organization (WHO) reports, about 8.6 million of people were infected with TB in 2013 [9, 10]. When a patient adopts bacterial resistance to the first-line drugs such as isoniazid, rifampicin, ethambutol, and pyrazinamide [11], health-threatening problems in the chemotherapy of TB arise, which seriously reduces the progress in anti-TB medical care.

In continuation of our research to design and synthesize bioactive heterocycles [12, 13], we have recently published the review on pharmacological potential of *s*-triazines [14], showing their important therapeutic applications as antibacterial [15], antifungal [16], antimycobacterial [17], anti-HIV [18], anticancer [19], and antiviral [20] agents. Compounds structurally related to *s*-triazine are also bioactive [21, 22].

In the present work, copper-catalyzed C-N coupling was introduced by using the Ullmann reaction approach [23, 24]. In the known successful C-N cross-coupling reactions [25, 26], palladium [27], nickel [28], and copper [23] catalysts have been used. To date, various modifications were attempted to develop improved conditions for C-N coupling [29–32]. The air-sensitive, toxic, and expensive reagents have been used in a Buchwald-Hartwig reaction [33–36], and one report describes a reaction conducted in water under ligand-free conditions [37]. Some mechanistic studies on copper-catalyzed arylation of a nucleophile have also been reported for C-N coupling reactions [38, 39]. In this work, we focused on the synthesis of copper-catalyzed trisubstituted triazine derivatives. The products were then screened for antimicrobial and antimycobacterial activities.

## Results and discussion

### Chemistry

The desired compounds **4a–j** and **5a–j** were synthesized by a series of reactions as shown in Scheme 1.

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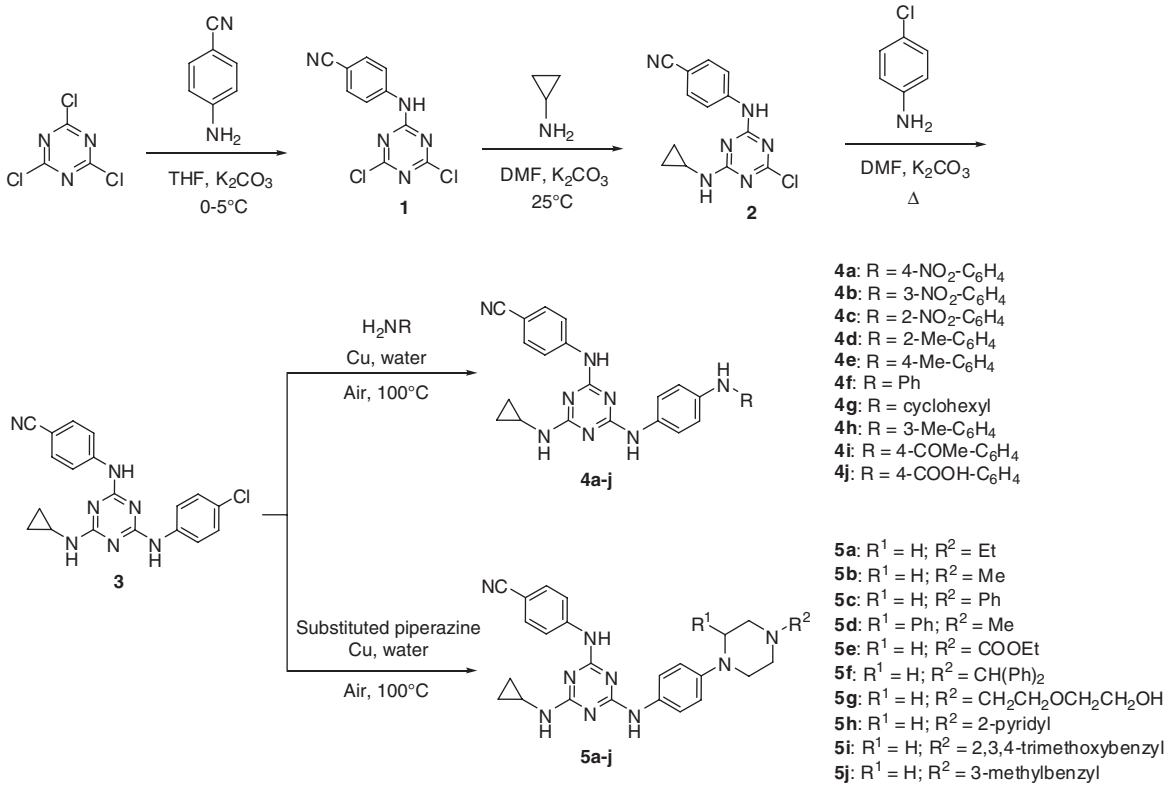


**Scheme 1** Synthetic route to compounds **4a–j** and **5a–j**.

The characteristic displacement of the first chloro atom of cyanuric chloride by 4-aminobenzonitrile has been reported in literature [20]. In this work, cyanuric chloride and 4-aminobenzonitrile in presence of $K_2CO_3$ were allowed to react in dry THF to yield 4-[(4,6-dichloro-1,3,5-triazin-2-yl)amino]benzonitrile (**1**). The intermediate 4-[(4-chloro-6-(cyclopropylamino)-1,3,5-triazin-2-yl) amino]benzonitrile (**2**) was synthesized by stirring **1** with cyclopropylamine and $K_2CO_3$ in dry DMF at 40–45°C for 4–5 h. The resulting compound **2** was further reacted to 4-chloroaniline in the presence of $K_2CO_3$ at reflux temperature to yield product **3**. The chlorophenyl moiety of **3** was coupled to various substituted amines and piperazines *via* Ullmann coupling reaction. The Cu-catalyzed C-N coupling was carried out in water under oxygen-free conditions under reflux to furnish the desired compounds **4a–j** and **5 a–j**. The structures of all intermediate and final products are fully consistent with the results of elemental analysis and analysis of spectral data.

## Biological evaluation

Selected *s*-triazine derivatives **4** and **5** were examined for their *in vitro* antimicrobial activity against two Gram-positive bacterial strains (*Staphylococcus aureus* MTCC 96 and *Bacillus cereus* MTCC 430), two Gram-negative bacterial strains (*Escherichia coli* MTCC 741 and *Salmonella typhi* MTCC 109), and two fungal strains (*Aspergillus niger* MTCC 1323 and *Aspergillus clavatus* MTCC 183) using agar dilution method [40]. Ciprofloxacin and streptomycin were used as standard control drugs for antibacterial activity, whereas griseofulvin was used as the standard control drug for antifungal activity. *In vitro* antitubercular activity was also performed for title compounds against the *M. tuberculosis* H37Rv strain by BACTEC MGIT method [41] using isoniazid, rifampicin, ethambutol, and pyrazinamide as standard control drugs. Some of the synthesized products were found to be potent against specific microbial strains.

### *In vitro* antibacterial activity

Table 1 shows that several *s*-triazines exhibit good to moderate activity against several microbial strains. It can be seen that compound **5b** bearing *N*-methyl piperazine moiety is the most potent analog that shows a 32-mm zone of inhibition and MIC of 1.56 μg/mL against *S. aureus* strain. This is an outstanding result when compared with the activity of penicillin (30 mm, 3.12 μg/mL) and streptomycin (28 mm, 6.25 μg/mL). Compound **5d** shows also good activity to inhibit the growth of *S. aureus* and *S. typhi*

**Table 1** *In vitro* antimicrobial activity of selected compounds **4** and **5**.

| Entry | Zone of inhibition (mm) (MIC, μg/mL) | | | | | |
|---|---|---|---|---|---|---|
| | Gram positive | | Gram negative | | Fungal strains | |
| | *S. aureus* | *B. cereus* | *E. coli* | *S. typhi* | *A. niger* | *A. clavatus* |
| **4e** | 12 (200) | 08 (25) | 20 (100) | 10 (3.12) | 15 (100) | 23 (100) |
| **4g** | 23 (6.25) | 22 (200) | 15 (3.12) | 11 (6.25) | 20 (200) | 20 (200) |
| **4i** | 27 (25) | 27 (3.12) | 24 (100) | 16 (12.5) | 19 (400) | 19 (400) |
| **5b** | **32 (1.56)**[b] | 12 (100) | 16 (400) | 24 (6.25) | 23 (100) | 19 (400) |
| **5d** | 28 (3.12) | 16 (50) | 17 (12.5) | 20 (3.12) | 12 (400) | 20 (100) |
| **5f** | 11 (400) | 13 (3.12) | 24 (400) | 18 (50) | 23 (100) | 15 (400) |
| **5g** | 18 (25) | 18 (50) | 21 (3.12) | 11 (12.5) | 20 (200) | 23 (100) |
| **5i** | 20 (6.25) | 26 (50) | 17 (50) | 07 (3.12) | 18 (200) | 15 (400) |
| Penicillin[a] | 30 (3.12) | 28 (1.56) | 26 (6.25) | 23 (12.5) | – | – |
| Streptomycin[a] | 28 (6.25) | 24 (6.25) | 23 (3.12) | 26 (3.12) | – | – |
| Griseofulvin[a] | – | – | – | – | 24 (100) | 23 (100) |

[a]Standard. [b]Superior inhibition profile.

bacteria. Derivatives **4i** and **5f** having electron withdrawing 4-acetyl and *N*-benzhydryl substituents exhibit half-fold (3.12 μg/mL) and equipotent (6.25 μg/mL) inhibition of *B. cereus* bacteria in comparison to activity of streptomycin (6.25 μg/mL). Against the *E. coli* strain, compounds **4g**, **5g**, and streptomycin show similar MIC. Compounds **4e** and **5i** demonstrate equipotent efficacy against *S. typhi* bacteria with penicillin (MIC, 12.5 μg/mL) and streptomycin (MIC, 3.12 μg/mL), respectively.

### *In vitro* antifungal activity

Antifungal activity data (Table 1) show that two compounds are highly active. These are compound **5b** and **4e** with electron-donating *N*-methylpiperazino and 4-methyl moieties that show the zone of inhibition of 23 mm against *A. niger* and *A. clavatus* fungi.

**Table 2** *In vitro* antitubercular activity of selected compounds **4** and **5**.

| Entry | BACTEC MGIT method[a] | |
|---|---|---|
| | MIC[b] | % Inhibition |
| **4a** | 6.25 | 92 |
| **4i** | 6.25 | 99 |
| **4j** | 6.25 | 94 |
| **5b** | **6.25**[c] | **99**[c] |
| **5g** | 6.25 | 96 |
| **5j** | >6.25 | 91 |
| Isoniazid | 0.20 | 99 |
| Refampicin | 0.25 | 99 |
| Ethambutol | 3.12 | 99 |
| Pyrazinamide | 6.25 | 99 |

[a]Each value is the mean of three independent experiment. [b]In μg/mL. [c]Superior inhibition profile.

### *In vitro* antitubercular activity

Table 2 indicates that the synthesized compounds are active against tubercular strain *M. tuberculosis* H37Rv strain.

## Conclusion

Two series of amino-substituted *s*-triazines **4a–j** and piperazino derivatives **5a–j** were synthesized by simple and efficient methods. Compounds were screened against a wide range of pathogenic bacteria, fungi, and H37Rv mycobacterial strains. Compound **5b** is the best bioactive derivative.

## Experimental

2,4,6-Trichloro-1,3,5-triazine, cyclopropylamine, and 4-aminobenzonitrile were purchased from Sigma-Aldrich. Acetone and tetrahydrofuran were purchased from Merck and used without further purification. Melting points of the products were determined in open capillaries using Veego electronic apparatus and are uncorrected. The IR spectra (4000–400 $cm^{-1}$) were recorded using KBr pellets. $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (100 MHz) spectra were recorded on Varian 400 spectrometer using DMSO-$d_6$ as a solvent.

### Synthesis of 4-[(4,6-dichloro-1,3,5-triazin-2-yl)amino] benzonitrile (1)

Potassium carbonate (14.9 g, 108 mmol) was slowly added at 0–5°C to a solution of cyanuric chloride (10 g, 54 mmol) and 4-aminobenzonitrile (6.41 g, 54 mmol) in dry THF (150 mL). The solution was stirred for 4–5 h at 0–5°C. After completion of the reaction based on TLC monitoring (toluene/acetone 7:3), the mixture was treated with crushed ice, followed by neutralization with dilute hydrochloric acid. The crude product **1** was then filtered, dried, and crystallized from acetone; yield 11.0 g (79%); mp 247–250°C; IR: 3277 (N-H), 2228 (C≡N), 833, 802 $cm^{-1}$; $^1H$ NMR: δ 8.61 (s, 1H, NH), 7.86–7.78 (m, 4H, Ar-H); $^{13}C$ NMR: δ 171.7 (triazine), 166.6 (triazine), 165.4 (triazine), 140.8 (Ar-C-NH), 132.2 (Ar-CH), 125.4 (Ar-CH), 122.6 (Ar-CH), 120.7 (Ar-CH), 119.3 (Ar-CN), 100.8 (Ar-C-CN); MS (ESI): *m/z* 265.94 [$M^+$]. Anal. Calcd for $C_{10}H_5Cl_2N_5$ (264.99): C, 45.14; H, 1.89; N, 26.32. Found: C, 45.11; H, 1.92; N, 26.34.

### Synthesis of 4-{[4-chloro-6-(cyclopropylamino)-1,3,5-triazin-2-yl]amino}benzonitrile (2)

A mixture of compound **1** (5 g, 18 mmol) and cyclopropylamine (1.07 g, 18 mmol) was stirred in dry DMF at room temperature. To this solution, $K_2CO_3$ (5.18 g, 37 mmol) was slowly added, and stirring was continued for 4–5 h, with the progress of the reaction monitored by TLC using hexanes/ethyl acetate (6:4) as an eluent. After completion of the reaction, the mixture was treated with crushed ice and neutralized with diluted hydrochloric acid. The precipitate was filtered, dried, and crystallized from methanol to afford desired compound **2**; yield 3.6 g (67%); mp 189–191°C; IR: 3357 (N-H), 2251 (C≡N), 846 (*s*-triazine), 789 $cm^{-1}$; $^1H$ NMR: δ 7.33 (d, *J* = 7 Hz, 2H, Ar-H), 7.06 (d, *J* = 7 Hz, 2H, Ar-H), 6.43 (s, 1H, NH), 3.46 (s, 1H, NH), 2.29 (m, 1H, CH), 1.10–0.63 (m, 4H, CH); $^{13}C$ NMR: δ 170.3 (triazine), 165.4 (triazine), 160.3 (triazine), 145.7 (Ar-C-NH), 133.2 (Ar-CH), 129.4 (Ar-CH), 123.2 (Ar-CH), 121.9 (Ar-CH), 117.0 (Ar-CN), 101.7 (Ar-C-CN), 22.4 (CH), 7.8 ($CH_2$), 7.5 ($CH_2$); MS (ESI): *m/z* 287.10 [$M^+$]. Anal. Calcd for $C_{13}H_{11}ClN_6$ (286.07): C, 54.46; H, 3.87; N, 29.31. Found: C, 54.43; H, 3.89; N, 29.35.

### Synthesis of 4-{[4-(4-chloroanilino)-6-(cyclopropylamino)-1,3,5-triazin-2-yl] amino}benzonitrile (3)

A mixture of compound **2** (5 g, 17 mmol) and 4-chloroaniline (2.21 g, 17 mmol) was heated under reflux in dry DMF for 3–4 h. Progress of the reaction was monitored by TLC using toluene/acetone (9:1) as an eluent. The mixture was treated with $K_2CO_3$ (4.69 g, 34 mmol) and poured onto crushed ice. The product **3** was filtered, dried, and crystallized from methanol; yield 4.6 g (71%); mp 164–166°C; IR: 3334 (N-H), 2851 (C-H aliphatic) 2291 (C≡N), 861 $cm^{-1}$; $^1H$ NMR: δ 7.48 (d, *J* = 7 Hz, 2H, Ar-H), 7.26–7.02 (m, 4H, Ar-H), 6.76 (d, *J* = 7 Hz, 2H, Ar-H), 6.49 (s, 1H, NH), 6.13 (s, 1H, NH), 3.61 (s, 1H, NH), 2.28 (m, 1H, CH), 1.30–0.59 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 168.2 (triazine), 165.1 (triazine), 158.6 (triazine), 148.8 (Ar-C-NH), 140.4 (Ar-C-NH), 133.6 (Ar-CH), 132.5 (Ar-CH), 131.6 (Ar-CH), 130.2 (Ar-CH), 129.1 (Ar-C-Cl), 123.7 (Ar-CH), 121.1 (Ar-CH), 121.0 (Ar-CH), 120.9 (Ar-CH), 117.6 (Ar-CN), 99.7 (Ar-C-CN), 22.6 (CH), 8.1 ($CH_2$), 7.9 ($CH_2$); MS (ESI): *m/z* 378.09 [$M^+$]. Anal. Calcd for $C_{19}H_{16}ClN_7$ (377.11): C, 60.40; H, 4.27; N, 25.95. Found: C, 60.38; H, 4.25; N, 25.94.

### General method for the preparation of compounds 4a–j and 5a–j

A mixture of compound **3** (5 mmol), 30% aqueous solution of a substituted amine or piperazine (5.4 mL, 27 mmol), and copper powder (10 mol%) was magnetically stirred at 100°C in a sealed tube. Progress of the reaction was monitored by TLC using hexanes/ethyl acetate (6:4) as an eluent. The mixture was cooled to room temperature and ethyl acetate (20 mL) was added to extract the product. The organic layer was separated, and the aqueous layer was additionally extracted with ethyl acetate (3×10 mL). The combined extracts were dried with anhydrous $Na_2SO_4$, and the solvent was removed under reduced pressure to give a crude product **4a–j** or **5a–j** that was purified by silica gel column chromatography.

**4-{[4-(Cyclopropylamino)-6-(4-(4-nitroanilino)anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (4a)** Yield 1.8 g (78%); mp 154–157°C; IR: 3365 (N-H), 3052 (C-H, aromatic), 2917 (C-H, aliphatic), 2652 (-$CH_2$, cyclopropylamine), 2268 (C≡N), 1533 ($NO_2$), 1362 (C-N), 851 $cm^{-1}$; $^1H$ NMR: δ 8.11 (d, *J* = 6 Hz, 2H, Ar-H), 7.81–7.12 (m, 4H, Ar-H), 7.02–6.86 (m, 6H, Ar-H), 6.58 (s, 1H, NH), 6.34 (s, 1H, NH), 6.15 (s, 1H, Ar-NH), 3.72 (s, 1H, NH), 2.87 (m, 1H, CH), 1.31–0.42 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 168.1, 162.6, 160.6 (*s*-triazine), 152.5, 149.2, 147.2, 145.1, 137.5, 134.5, 130.3, 127.2, 126.1, 118.1, 113.3, 103.8 (Ar-C), 119.2 (Ar-CN), 24.48 (CH), 6.92 (2C, $CH_2$); MS (ESI): *m/z* 480.42 [$M^+$]. Anal. Calcd for $C_{25}H_{21}N_9O_2$ (479.49): C, 62.62; H, 4.41; N, 26.29. Found: C, 62.56; H, 4.42; N, 26.23.

**4-{[4-(Cyclopropylamino)-6-(4-(3-nitroanilino)anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (4b)** Yield 1.5 g (64%); mp 137–142°C; IR: 3435 (N-H), 3095 (C-H, aromatic), 2920 (C-H, aliphatic), 2667 ($CH_2$, cyclopropylamine), 2222 (C≡N), 1518 ($NO_2$), 1346 (C-N), 869 $cm^{-1}$; $^1H$ NMR: δ 7.96 (d, *J* = 7 Hz, 1H, Ar-H), 7.89–7.38 (m, 4H, Ar-H), 7.28–6.98 (m, 7H, Ar-H), 6.34 (s, 1H, NH), 6.14 (s, 1H, NH), 5.87 (s, 1H, Ar-NH), 3.51 (s, 1H, NH), 3.14 (m, 1H, CH), 1.14–0.33 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 169.9, 166.1, 162.3 (*s*-triazine), 155.2, 150.0, 148.7, 146.2, 138.3, 135.5, 132.7, 129.8, 128.1, 123.1, 119.3, 115.7, 111.7, 107.0 (Ar-C), 119.9 (Ar-CN), 23.5 (CH), 6.29 (2C, $CH_2$); MS (ESI): *m/z* 480.61 [$M^+$]. Anal. Calcd for $C_{25}H_{21}N_9O_2$ (479.49): C, 62.62; H, 4.41; N, 26.29. Found: C, 62.48; H, 4.40; N, 26.35.

**4-{[4-(Cyclopropylamino)-6-(4-(2-nitroanilino)anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (4c)** Yield 1.4 g (61%); mp 122–125°C; IR: 3458 (N-H, secondary), 3064 (C-H, aromatic), 2932 (C-H, aliphatic), 2699 ($CH_2$), 2232 (C≡N), 1552 ($NO_2$), 1301 (C-N), 858 $cm^{-1}$; $^1H$ NMR: δ 8.14 (d, *J* = 7 Hz, 1H, Ar-H), 7.97–7.52 (m, 4H, Ar-H), 7.417.15 (m, 7H, Ar-H), 6.34 (s, 1H, NH), 6.31 (s, 1H, NH), 6.04 (s, 1H, Ar-NH), 3.45 (s, 1H, NH), 3.03 (m, 1H, CH), 1.32–0.21 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 165.8, 164.4, 158.5 (*s*-triazine), 152.4, 151.2, 147.1, 145.4, 139.6, 132.1, 130.3, 128.8, 125.9, 122.0, 119.5, 114.4, 110.4, 104.5 (Ar-C), 120.7 (Ar-CN), 25.6 (CH), 7.6 ($CH_2$); MS (ESI): *m/z* 480.49 [$M^+$]. Anal. Calcd for $C_{25}H_{21}N_9O_2$ (479.49): C, 62.62; H, 4.41; N, 26.29. Found: C, 62.79; H, 4.42; N, 26.22.

**4-{[4-(Cyclopropylamino)-6-(4-(*o*-tolylamino)anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (4d)** Yield 1.7 g (79%); mp 200–203°C; IR: 3391 (N-H, secondary), 3047 (C-H, aromatic), 2966 (C-H,

aliphatic), 2640 (-$CH_2$, cyclopropylamine), 2201 (C≡N), 1316 (C-N stretch), 868 $cm^{-1}$; $^1H$ NMR: δ 8.20 (d, *J* = 7 Hz, 1H, Ar-H), 7.82–7.60 (m, 4H, Ar-H), 7.53–7.24 (m, 7H, Ar-H), 6.64 (s, 1H, NH), 6.40 (s, 1H, NH), 6.17 (s, 1H, Ar-NH), 3.18 (s, 1H, NH), 2.97 (m, 1H, CH), 2.31 (s, 3H, $CH_3$), 1.43–0.13 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 166.4, 162.5, 160.2 (*s*-triazine), 153.6, 150.4, 147.3, 144.7, 138.1, 135.8, 132.5, 129.2, 126.7, 120.2, 118.5, 115.4, 111.4, 106.2 (Ar-C), 119.4 (Ar-CN), 24.2 (CH), 16.5 (Ar-$CH_3$), 8.1 ($CH_2$); MS (ESI): *m/z* 449.50 [$M^+$]. Anal. Calcd for $C_{26}H_{24}N_8$ (448.52): C, 69.62; H, 5.39; N, 24.98. Found: C, 69.49; H, 5.38; N, 24.95.

**4-{[4-(Cyclopropylamino)-6-(4-(*p*-tolylamino)anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (4e)** Yield 1.3 g (58%); mp 148–151°C; IR: 3452 (N-H, secondary), 3031 (C-H, aromatic), 2932 (C-H, aliphatic), 2618 (-$CH_2$, cyclopropylamine), 2249 (C≡N), 1349 (C-N), 818 $cm^{-1}$; $^1H$ NMR: δ 8.14 (d, *J* = 7 Hz, 1H, Ar-H), 7.96–7.68 (m, 4H, Ar-H), 7.57–7.31 (m, 7H, Ar-H), 6.72 (s, 1H, NH), 6.38 (s, 1H, NH), 6.18 (s, 1H, Ar-NH), 3.36 (s, 1H, NH), 3.04 (m, 1H, CH), 2.66 (s, 3H,$CH_3$), 1.42–0.27 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 164.4, 161.5, 160.6 (*s*-triazine), 151.2, 150.6, 148.5, 143.8, 139.7, 133.3, 130.1, 129.7, 124.5, 117.8, 112.1, 104.2 (Ar-C), 119.2 (Ar-CN), 25.2 (CH), 14.1 (Ar-$CH_3$), 7.5 ($CH_2$); MS (ESI): *m/z* 449.52 [$M^+$]. Anal. Calcd for $C_{26}H_{24}N_8$ (448.52): C, 69.62; H, 5.39; N, 24.98. Found: C, 69.44; H, 5.37; N, 24.93.

**4-{[4-(Cyclopropylamino)-6-(4-(anilino)anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (4f)** Yield 1.7 g (80%); mp 122–125°C; IR: 3432 (N-H, secondary), 3064 (C-H, aromatic), 2984 (C-H, aliphatic), 2632 (-$CH_2$, cyclopropylamine), 2294 (C≡N), 1354 (C-N), 842 $cm^{-1}$; $^1H$ NMR: δ 7.84–7.63 (m, 4H, Ar-H), 7.48–7.25 (m, 5H, Ar-H), 7.15–6.84 (m, 4H, Ar-H), 6.57 (s, 1H, NH), 6.28 (s, 1H, NH), 6.02 (s, 1H, Ar-NH), 3.45 (s, 1H, NH), 3.24 (m, 1H, CH), 1.24–0.27 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 165.73, 162.48, 159.17 (*s*-triazine), 153.2 152.6 149.3, 142.3, 138.4, 135.5, 131.1, 128.6, 123.2, 118.4, 115.8, 105.8 (Ar-C), 119.9 (Ar-CN), 26.5 (CH), 6.3 ($CH_2$); MS (ESI): *m/z* 435.41 [$M^+$]. Anal. Calcd for $C_{25}H_{22}N_8$ (434.50): C, 69.11; H, 5.10; N, 25.79. Found: C, 69.08; H, 5.09; N, 25.72.

**4-{[4-(4-(Cyclohexylamino)anilino)-6-(cyclopropylamino)-1,3,5-triazin-2-yl]amino}benzonitrile (4g)** Yield 1.3 g (63%); mp 197–199°C; IR: 3412 (N-H, secondary), 3054 (C-H, aromatic), 2956 (C-H, aliphatic), 2632 ($CH_2$, cyclopropylamine), 2154 (C≡N), 1354 (C-N), 832 $cm^{-1}$; $^1H$ NMR: δ 7.26–6.98 (m, 4H, Ar-H), 6.90–6.85 (m, 4H, Ar-H), 6.64 (s, 1H, NH), 6.38 (s, 1H, NH), 6.21 (s, 1H, Ar-NH), 4.12 (s, 1H, NH), 3.84 (m, 1H, CH), 3.21 (m, 1H, -CH), 1.83 (m, 4H, $CH_2$), 1.66 (m, 6H, $CH_2$), 1.36–0.16 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 164.3, 161.1, 158.4 (*s*-triazine), 148.6, 145.1, 135.6, 131.6, 125.9, 122.4, 116.6, 104.1 (12 C, Ar-C), 120.3 (Ar-CN), 56.8 (CH), 38.5 ($CH_2$), 28.3 ($CH_2$), 25.82 ($CH_2$), 24.90 (CH), 7.26 ($CH_2$); MS (ESI): *m/z* 441.54 [$M^+$]. Anal. Calcd for $C_{25}H_{28}N_8$ (440.54): C, 68.16; H, 6.41; N, 25.44. Found: C, 68.25; H, 6.39; N, 25.47.

**4-{[4-(Cyclopropylamino)-6-(4-(*m*-tolylamino)anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (4h)** Yield 1.5 g (70%); mp 161–164°C; IR: 3462 (N-H, secondary), 3031 (C-H, aromatic), 2902 (C-H, aliphatic), 2621 ($CH_2$, cyclopropylamine), 2264 (C≡N), 1354 (C-N), 835 $cm^{-1}$; $^1H$ NMR: δ 7.96 (d, *J* = 7 Hz, 1H, Ar-H), 7.58–7.36 (m, 4H, Ar-H), 7.24–7.08 (m, 7H, Ar-H), 6.86 (s, 1H, NH), 6.52 (s, 1H, NH), 6.27 (s, 1H, Ar-NH), 3.89 (s, 1H, NH), 3.16 (m, 1H, CH), 2.45 (s, 3H, $CH_3$), 1.43–0.13 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 168.1, 163.4, 159.6 (*s*-triazine), 152.5, 150.2, 145.6, 142.3, 139.9, 134.3, 131.4, 128.4, 125.5, 121.6, 117.3, 112.2, 110.2, 103.9 (Ar-C), 118.7 (Ar-CN), 25.6 (CH,), 15.42 (Ar-$CH_3$), 7.76 ($CH_2$); MS (ESI): *m/z* 449.52 [$M^+$]. Anal. Calcd for $C_{26}H_{24}N_8$ (448.52): C, 69.62; H, 5.39; N, 24.98. Found: C, 69.47; H, 5.40; N, 24.92.

**4-{[4-(4-(4-Acetylanilino)anilino)-6-(cyclopropylamino)-1,3,5-triazin-2-yl]amino}benzonitrile (4i)** Yield 1.3 g (58%); mp 119–122°C; IR: 3344 (N-H), 3042 (C-H, aromatic), 2911 (C-H, aliphatic), 2632 ($CH_2$, cyclopropylamine), 2261 (C≡N), 1695 (C=O), 1322 (C-N), 820 $cm^{-1}$; $^1H$ NMR: δ 8.24 (d, *J* = 7 Hz, 2H, Ar-H), 7.97–7.75 (m, 4H, Ar-H), 7.61–7.43 (m, 6H, Ar-H), 6.87 (s, 1H, NH), 6.56 (s, 1H, NH), 6.29 (s, 1H, Ar-NH), 4.09 (s, 1H, NH), 3.35 (m, 1H, CH), 2.87 (s, 3H, $CH_3$), 1.43–0.18 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 193.6 (CO-$CH_3$), 166.2, 164.9, 159.3 (*s*-triazine), 154.5, 148.7, 145.3, 140.7, 137.2, 134.3, 130.3, 128.9, 122.4, 118.8, 111.7, 103.1 (Ar-C), 119.3 (Ar-CN), 28.6 (CO-$CH_3$), 24.9 (CH,), 7.48 ($CH_2$); MS (ESI): *m/z* 477.53 [$M^+$]. Anal. Calcd for $C_{27}H_{24}N_8O$ (476.53): C, 68.05; H, 5.08; N, 23.51. Found: C, 68.25; H, 5.07; N, 23.55.

**4-{[4-(4-(4-Cyanoanilino)-6-(cyclopropylamino)-1,3,5-triazin-2-yl]amino}benzoic acid (4j)** Yield 1.5 g (66%); mp 161–164°C; IR: 3497 (-COOH), 3470 (N-H, secondary), 3032 (C-H, aromatic), 2931 (C-H, aliphatic), 2645 ($CH_2$, cyclopropylamine), 2201 (C≡N), 1708 (C=O), 1317 (C-N), 802 $cm^{-1}$; $^1H$ NMR: δ 11.24 (s, 1H, COOH), 8.05 (d, *J* = 7 Hz, 2H, Ar-H), 7.84–7.62 (m, 4H, Ar-H), 7.55–7.39 (m, 6H, Ar-H), 6.76 (s, 1H, NH), 6.47 (s, 1H, NH), 6.22 (s, 1H, Ar-NH), 3.86 (s, 1H, NH), 3.28 (m, 1H, CH), 1.21–0.35 (m, 4H, -$CH_2$); $^{13}C$ NMR: δ 169.5 (COOH), 163.4, 160.8, 158.2 (*s*-triazine), 150.7, 148.1, 145.9, 144.1, 137.5, 134.7, 131.9, 127.1, 125.7, 118.4, 115.5, 101.1 (Ar-C), 120.2 (Ar-CN), 24.9 (CH), 6.9 ($CH_2$); MS (ESI): *m/z* 479.53 [$M^+$]. Anal. Calcd for $C_{26}H_{22}N_8O_2$ (478.51): C, 65.26; H, 4.63; N, 23.42. Found: C, 65.16; H, 4.62; N, 23.46.

**4-{[4-(Cyclopropylamino)-6-(4-(4-ethylpiperazino) anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (5a)** Yield 1.6 g (70%); mp 124–126°C; IR: 3392 (N-H, secondary), 3149 (C-H, aromatic), 2933 (C-H, aliphatic), 2810 (-$CH_2$, cyclopropylamine), 2220 (C≡N), 1359 (C-N), 835 $cm^{-1}$; $^1H$ NMR: δ 8.11 (d, *J* = 7 Hz, 2H, Ar-H), 7.83–7.67 (m, 4H, Ar-H), 7.53–7.31 (m, 2H, Ar-H), 6.98 (s, 1H, NH), 6.52 (s, 1H, Ar-NH), 3.68 (s, 1H, NH), 3.08 (m, 4H, $CH_2$), 2.79 (m, 4H, $CH_2$), 2.45–2.38 (m, 3H, CH), 1.21 (t, *J* = 7 Hz, 3H, $CH_3$), 1.01–0.71 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 165.1, 164.0, 163.6 (*s*-triazine), 145.2, 144.7, 139.1, 132.7, 128.4, 125.3, 121.3, 102.2 (Ar-C), 119.5 (Ar-CN), 52.3 (piperazine), 51.6 (piperazine), 51.0 ($CH_2$), 23.5 (CH), 11.9 ($CH_3$), 6.3 ($CH_2$); MS (ESI): *m/z* 456.31 [$M^+$]. Anal. Calcd for $C_{25}H_{29}N_9$ (455.56): C, 65.91; H, 6.42; N, 27.67. Found: C, 66.06; H, 6.40; N, 27.60.

**4-{[4-(Cyclopropylamino)-6-(4-(4-methylpiperazino) anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (5b)** Yield 1.4 g (64%); mp 183–185°C; IR: 3340 (N-H, secondary), 3159 (C-H, aromatic), 2914 (C-H, aliphatic), 2864 ($CH_2$, cyclopropylamine), 2222 (C≡N), 1367 (C-N), 869 $cm^{-1}$; $^1H$ NMR: δ 7.91 (d, *J* = 7 Hz, 2H, Ar-H), 7.76–7.52 (m, 4H, Ar-H), 7.47–7.21 (m, 2H, Ar-H), 6.47 (s, 1H, NH), 6.26 (s, 1H, Ar-NH), 3.88 (s, 1H, NH), 3.34 (m, 4H, $CH_2$), 2.94 (m, 4H, $CH_2$), 2.38 (m, 1H, CH), 1.87 (s, 3H, $CH_3$), 1.31–0.46 (m, 4H, $CH_2$); $^{13}C$ NMR: δ 166.4, 163.6, 160.4 (*s*-triazine), 148.7, 145.6, 138.1, 135.9, 129.4, 127.2, 120.8, 101.2 (Ar-C), 119.1 (Ar-CN), 50.4 (piperazine), 49.9 (, piperazine), 47.1 ($CH_3$), 24.9 (CH), 7.24 (2C, $CH_2$,); MS (ESI): *m/z* 442.54 [$M^+$]. Anal. Calcd for $C_{24}H_{27}N_9$ (441.53): C, 65.29; H, 6.16; N, 28.55. Found: C, 65.11; H, 6.14; N, 28.47.

**4-{[4-(Cyclopropylamino)-6-(4-(4-phenylpiperazino) anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (5c)** Yield 1.9 g (76%); mp 167–169°C; IR: 3318 (N-H, secondary), 3172 (C-H, aromatic), 2946 (C-H, aliphatic), 2833 ($CH_2$, cyclopropylamine), 2216 (C≡N), 1334 (C-N), 866 $cm^{-1}$; $^1H$ NMR: δ 7.78 (d, *J* = 7 Hz, 2H, Ar-H), 7.57–7.36 (m, 5H, Ar-H), 7.14–6.83 (m, 6H, Ar-H), 6.38 (s, 1H, NH), 6.14 (s, 1H, Ar-NH),

3.46 (s, 1H, NH), 3.25 (m, 4H, $CH_2$), 2.84 (m, 4H, $CH_2$), 2.55 (m, 1H, CH), 1.24–0.27 (m, 4H, $CH_2$); $^{13}$C NMR: δ 164.4, 162.1, 161.6 (*s*-triazine), 151.8, 146.6, 142.9, 139.5, 133.4, 130.4, 129.1, 126.6, 122.3, 121.7, 120.1, 117.9, 101.5 (Ar-C), 119.6 (Ar-CN), 51.2(piperazine), 48.6 (piperazine), 22.9 (CH), 8.1 ($CH_2$); MS (ESI): *m/z* 504.58 [$M^+$]. Anal. Calcd for $C_{29}H_{29}N_9$ (503.60): C, 69.16; H, 5.80; N, 25.03. Found: C, 69.06; H, 5.82; N, 25.00.

**4-{[4-(Cyclopropylamino)-6-(4-(4-methyl-2-phenylpiperazino) anilino)-1,3,5-triazin-2-yl)]amino}benzonitrile (5d)** Yield 2.0 g (79%); mp 142–144°C; IR: 3310 (N-H, secondary), 3124 (C-H, aromatic), 2957 (C-H, aliphatic), 2864 (-$CH_2$, cyclopropylamine), 2245 (C≡N), 1368 (C-N), 847 $cm^{-1}$; $^1$H NMR: δ 8.12 (d, *J* = 7 Hz, 2H, Ar-H), 7.96–7.72 (m, 6H, Ar-H), 7.12–6.95 (m, 5H, Ar-H), 6.47 (s, 1H, NH), 6.10 (s, 1H, Ar-NH), 4.87 (t, 1H, *J* = 4 Hz, $CH_2$), 3.84 (dt, 2H, *J* = 4 Hz, -$CH_2$), 3.43 (s, 1H, NH), 2.84–2.67 (m, 4H, $CH_2$), 2.51 (s, 3H, $CH_3$), 2.14 (m, 1H, CH), 1.46–0.23 (m, 4H, $CH_2$); $^{13}$C NMR: δ 162.58, 161.47, 160.18 (*s*-triazine), 148.8, 145.3, 143.5, 135.9, 130.4, 129.2, 128.6, 127.5, 125.1, 122.7, 121.2, 103.1 (Ar-C), 119.8 (Ar-CN), 62.5 (CH), 58.9 ($CH_2$), 50.8 ($CH_2$), 48.2 ($CH_2$,), 45.6 ($CH_3$), 24.18 (CH), 6.47 (2C, $CH_2$); MS (ESI): *m/z* 518.60 [$M^+$]. Anal. Calcd for $C_{30}H_{31}N_9$ (517.63): C, 69.61; H, 6.04; N, 24.35. Found: C, 69.46; H, 6.03; N, 24.37.

**Ethyl 4-{4-[4-(4-cyanoanilino)-6-(cyclopropylamino)-1,3,5-triazin-2-yl)amino]phenyl}piperazine-1-carboxylate (5e)** Yield 2.0 g (81%); mp 198–201°C; IR: 3392 (N-H, secondary), 3172 (C-H, aromatic), 2964 (C-H, aliphatic), 2834 (-$CH_2$), 2279 (C≡N), 1740 (COO-), 1334 (C-N), 818 $cm^{-1}$; $^1$H NMR: δ 7.96 (d, *J* = 7 Hz, 2H, Ar-H), 7.74–7.53 (m, 4H, Ar-H), 7.37–7.22 (m, 2H, Ar-H), 6.96 (s, 1H, NH), 6.45 (s, 1H, Ar-NH), 4.25 (m, 2H, $CH_2$), 3.73 (s, 1H, NH), 3.47 (m, 4H, $CH_2$), 2.66 (m, 4H, $CH_2$), 2.28 (m, 1H, CH), 1.73–0.41 (m, 7H, CH); $^{13}$C NMR: δ 166.18, 165.61, 162.33 (*s*-triazine), 156.42 (CO), 148.2, 145.6, 138.2, 131.1, 129.7, 126.9, 122.1, 101.6 (Ar-C), 118.9 (Ar-CN), 63.9 ($CH_2$), 49.3 (piperazine), 44.3 (piperazine), 24.4 (CH), 15.9 ($CH_3$), 8.13 ($CH_2$); MS (ESI): *m/z* 500.52 [$M^+$]. Anal. Calcd for $C_{26}H_{29}N_9O_2$ (499.57): C, 62.51; H, 5.85; N, 25.23. Found: C, 62.33; H, 5.83; N, 25.17.

**4-{[(4-(4-Diphenylmethyl)piperazino)anilino)-6-(cyclopropylamino)-1,3,5-triazin-2-yl]amino}benzonitrile (5f)** Yield 1.6 g (55%); mp 133–135°C; IR: 3311 (N-H), 3146 (C-H, aromatic), 2912 (C-H, aliphatic), 2832 ($CH_2$), 2248 (C≡N), 1392 (C-N), 818 $cm^{-1}$; $^1$H NMR: δ 8.13–7.83 (m, 6H, Ar-H), 7.61–7.42 (m, 7H, Ar-H), 7.12–6.62 (m, 5H, Ar-H), 6.25 (s, 1H, NH), 6.13 (s, 1H, Ar-NH), 5.31 (s, 1H, CH), 3.93 (s, 1H, NH), 3.25 (m, 4H, $CH_2$), 2.66 (m, 4H, $CH_2$), 2.12 (m, 1H, CH), 1.24–0.15 (m, 4H, $CH_2$); $^{13}$C NMR: δ 162.3, 161.7, 160.3 (*s*-triazine), 149.2, 148.7, 142.8, 135.4, 131.2, 129.8, 127.8, 125.4, 125.0, 123.6, 121.5, 103.7 (Ar-C), 119.2 (Ar-CN), 79.5 (CH), 52.7 (piperazine), 50.4 (piperazine), 22.7 (CH), 6.9 ($CH_2$); MS (ESI): *m/z* 592.75 [$M^+$]. Anal. Calcd for $C_{36}H_{35}N_9$ (593.72): C, 72.83; H, 5.94; N, 21.23. Found: C, 72.95; H, 5.96; N, 21.17.

**4-{[4-(Cyclopropylamino)-6-(4-(4-(2-(2-hydroxyethoxy)ethyl) piperazino)anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (5g)** Yield 1.5 g (59%); mp 218–219°C; IR: 3498 (OH), 3364 (N-H, secondary), 3124 (C-H, aromatic), 2979 (C-H, aliphatic), 2857 ($CH_2$), 2216 (C≡N), 1346 (C-N), 834 $cm^{-1}$; $^1$H NMR: δ 7.68 (d, *J* = 7 Hz, 2H, Ar-H), 7.42–7.27 (m, 4H, Ar-H), 6.94–6.54 (m, 2H, Ar-H), 6.31 (s, 1H, NH), 6.18 (s, 1H, Ar-NH), 4.25 (s, 1H, NH), 4.05 (s, 1H, OH), 3.78–3.50 (m, 6H, $CH_2$), 3.26 (m, 4H, $CH_2$), 2.83 (m, 4H, $CH_2$), 2.57 (t, *J* = 5 Hz, 2H, $CH_2$), 2.15 (m, 1H, CH), 1.62–0.38 (m, 4H, $CH_2$); $^{13}$C NMR: δ 164.6, 162.4, 161.2 (*s*-triazine), 149.2, 142.1, 134.4, 131.6, 126.1, 124.8, 121.4, 103.1 (Ar-C), 120.9 (Ar-CN), 71.9 (O-$CH_2$), 68.6 ($CH_2O$), 63.0 ($CH_2OH$), 57.3 ($NCH_2$), 51.4 (piperazine), 48.7 (piperazine), 23.2 (CH), 8.8 ($CH_2$); MS (ESI): *m/z* 516.55 [$M^+$]. Anal. Calcd for $C_{27}H_{33}N_9O_2$ (515.61): C, 62.89; H, 6.45; N, 24.45. Found: C, 62.74; H, 6.44; N, 24.49.

**4-{[4-(Cyclopropylamino)-6-(4-(4-(pyridin-2-yl)piperazino) anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (5h)** Yield 1.9 g (77%); mp 171–174°C; IR: 3364 (N-H, secondary), 3124 (C-H, aromatic), 2967 (C-H, aliphatic), 2856 ($CH_2$), 2224 (C≡N), 1370 (C-N), 810 $cm^{-1}$; $^1$H NMR: δ 8.24 (d, *J* = 7 Hz, 1H, Ar-H), 7.83 (d, *J* = 7 Hz, 2H, Ar-H), 7.69–7.48 (m, 5H, Ar-H), 7.12–6.60 (m, 4H, Ar-H), 6.33 (s, 1H, NH), 6.05 (s, 1H, Ar-NH), 4.16 (s, 1H, NH), 3.41 (m, 4H, $CH_2$), 2.57 (m, 4H, $CH_2$), 2.22 (m, 1H, CH), 1.29–0.33 (m, 4H, $CH_2$); $^{13}$C NMR: δ 164.6, 162.3, 161.1 (*s*-triazine), 159.2, 148.6, 141.9, 112.7, 108.3 (pyridine), 147.8, 142.1, 134.9, 131.7, 126.6, 122.2, 120.2, 103.0 (Ar-C), 118.3 (Ar-CN), 51.7 (piperazine), 48.2 (piperazine), 23.2 (CH), 8.1 ($CH_2$); MS (ESI): *m/z* 505.45 [$M^+$]. Anal. Calcd for $C_{28}H_{28}N_{10}$ (504.59): C, 66.65; H, 5.59; N, 27.76. Found: C, 66.48; H, 5.57; N, 27.69.

**4-{[4-(Cyclopropylamino)-6-(4-(4-(2,3,4-trimethoxybenzyl)piperazino)anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (5i)** Yield 2.0 g (69%); mp 209–211°C; IR: 3346 (N-H, secondary), 3112 (C-H, aromatic), 2997 (C-H, aliphatic), 2846 (-$CH_2$, cyclopropylamine), 2245 (C≡N), 1324 (C-N stretch), 853 $cm^{-1}$; $^1$H NMR: δ 7.82 (d, *J* = 7 Hz, 2H, Ar-H), 7.55–7.23 (m, 4H, Ar-H), 7.11–6.44 (m, 4H, Ar-H), 6.25 (s, 1H, NH), 6.15 (s, 1H, Ar-NH), 3.92 (s, 6H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 3.63 (s, 1H, NH), 3.51 (s, 2H, $CH_2$), 3.28 (m, 4H, $CH_2$), 2.85 (m, 4H, $CH_2$), 2.49 (m, 1H, CH), 1.18–0.36 (m, 4H, $CH_2$); $^{13}$C NMR: δ 164.3, 162.1, 161.6 (*s*-triazine), 156.4, 152.7, 149.2, 143.1, 142.9, 135.1, 131.9, 127.1, 126.7, 124.2, 122.6, 120.4, 110.8, 104.9 (Ar-C), 118.3 (Ar-CN), 64.3 ($OCH_3$), 63.5 ($OCH_3$), 60.6 ($CH_2$), 57.7 ($OCH_3$), 49.4 (piperazine), 47.8 (piperazine), 25.8 (CH), 8.2 ($CH_2$); MS (ESI): *m/z* 608.64 [$M^+$]. Anal. Calcd for $C_{33}H_{37}N_9O_3$ (607.71): C, 65.22; H, 6.14; N, 20.74. Found: C, 65.29; H, 6.15; N, 20.68.

**4-{[4-(Cyclopropylamino)-6-(4-(4-(3-methylbenzyl)piperazino) anilino)-1,3,5-triazin-2-yl]amino}benzonitrile (5j)** Yield 1.5 g (58%); mp 181–183°C; IR: 3346 (N-H, secondary), 3117 (C-H, aromatic), 2946 (C-H, aliphatic), 2812 (-$CH_2$, cyclopropylamine), 2215 (C≡N), 1360 (C-N), 844 $cm^{-1}$); $^1$H NMR: δ 8.14 (d, *J* = 7 Hz, 2H, Ar-H), 7.85–7.69 (m, 5H, Ar-H), 7.32–7.05 (m, 5H, Ar-H), 6.23 (s, 1H, NH), 6.10 (s, 1H, Ar-NH), 3.63 (s, 1H, NH), 3.42 (s, 2H, $CH_2$), 3.28 (m, 4H, $CH_2$), 2.85 (m, 4H, $CH_2$), 2.41 (m, 1H, CH), 2.10 (s, 3H, $CH_3$), 1.26–0.50 (m, 4H, -$H_2$); $^{13}$C NMR: δ 163.2, 161.3, 159.7 (*s*-triazine), 149.9, 144.5, 138.1, 136.4, 133.3, 131.7, 129.9, 127.7, 127.2, 126.7, 125.3, 123.7, 121.2, 104.1 (Ar-C), 120.6 (Ar-CN), 67.1 ($CH_2$), 51.3 (piperazine), 48.7 (piperazine), 25.9 (CH), 22.7 ($CH_3$), 6.3 ($CH_2$); MS (ESI): *m/z* 532.42 [$M^+$]. Anal. Calcd for $C_{31}H_{33}N_9$ (531.65): C, 70.03; H, 6.26; N, 23.71. Found: C, 70.08; H, 6.24; N, 23.77.

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