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Synthesis, characterization, and antimicrobial screening of *s*-triazines linked with piperazine or aniline scaffolds

Abstract: Two series of *s*-triazines linked with piperazine or aniline scaffolds (**4a–i** and **5a–j**) were synthesized and evaluated for their *in vitro* biological efficacy against Gram positive and Gram negative bacteria (*Klebsiella pneumoniae* MTCC 109, *Pseudomonas aeruginosa* MTCC 741, *Staphylococcus aureus* MTCC 96, *Bacillus cereus* MTCC 619) and fungi (*Candida albicans* MTCC 183 and *Aspergillus niger* MTCC 282) using a broth dilution technique. Compounds most active against certain bacteria and fungi are **4e**, **4g**, **4i**, **5d**, and **5i**.

Keywords: aniline; antimicrobial screening; piperazine; *s*-triazine.

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Introduction

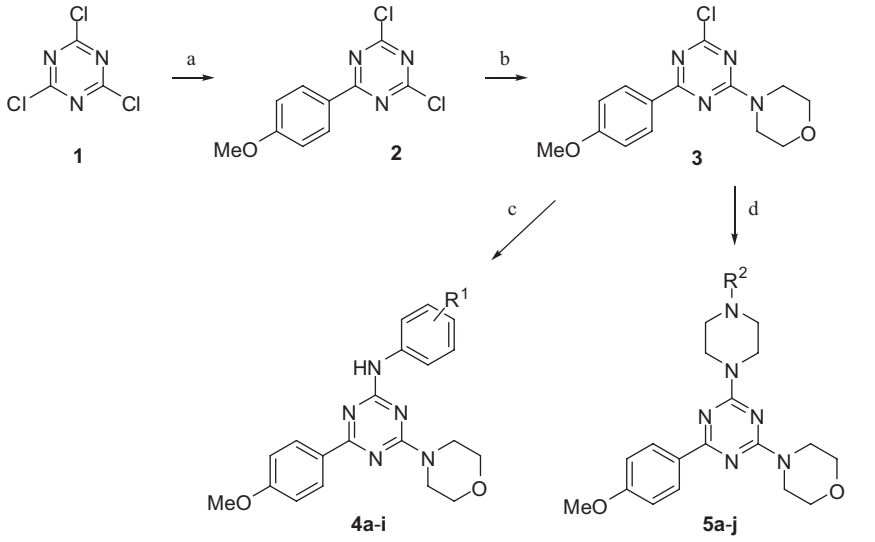
Drug-resistant strength of various disease-causing microbes to well-known antibiotics has increased in recent decades. Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was originally sensitive. Resistant organisms (they include bacteria, fungi, viruses, and some parasites) are able to withstand attack by antimicrobial medicines, such as antibiotics, antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist, increasing the risk of spread. Some infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA). According to the World Health Organization (WHO), approximately 8.7 million people have been infected and 1.4 million people have died from tuberculosis (TB) in the year 2011 [1]. Diseases caused by resistant microbial flora often fail to respond to standard drug treatment, resulting in prolonged illness and greater risk of death. The achievements of novel drugs are put at risk by AMR. Without efficient antimicrobials for care and avoidance of infections, the success of treatments such as organ transplantation, cancer chemotherapy, and major surgery would be compromised. Infections caused by resistant microorganisms pose a serious challenge to the medical community and the need for an effective therapy has led to a search for novel antimicrobial agents.

According to a literature survey, many *s*-triazine derivatives have been found to possess good antimicrobial properties and diverse pharmacological activities showing broadly active herbicidal [2] and antimicrobial [3] properties. Some are also used for the treatment of HIV infection [4–6]. Several workers have investigated *s*-triazine derivatives in the scope of potential therapeutic agents for diseases due to bacteria [7–10], cancer [11–13], antitumor [14, 15], and malaria [16, 17]. This literature survey led us to consider the *s*-triazine system as a possible scaffold. Various substituted piperazine and aniline derivatives linked with *s*-triazine moiety possess potential antimicrobial [18], antituberculosis [18], and antimalarial [19, 20] activity. Several morpholine-substituted *s*-triazine derivatives also display good biological activity.

Results and discussion

Chemistry

The desired compounds **4a–i** and **5a–j** were synthesized as outlined in Scheme 1. This synthetic route is practical, amendable to scale-up, and offers a general modus operandi for the preparation of a diversity of *s*-triazine derivatives. Synthesis of compound **2** was achieved by the treatment of cyanuric chloride (**1**) with anisole in the presence of $AlCl_3$. The next step to compound **3** was a nucleophilic displacement of the second chloride in compound **2** by the reaction with morpholine in the presence of sodium bicarbonate. The third chloride was replaced by the reaction of **3** with aniline, substituted aniline, piperazine, or substituted piperazine. All synthesized compounds were



4a: R^1 = H
4b: R^1 = 3-NO_2
4c: R^1 = 4-NO_2
4d: R^1 = 2-Cl
4e: R^1 = 3-Cl
4f: R^1 = 4-Cl
4g: R^1 = 2-Me
4h: R^1 = 3-Me
4i: R^1 = 4-Me
5a: R^2 = H
5b: R^2 = Me
5c: R^2 = Et
5d: R^2 = OCOMe
5e: R^2 = 3-Cl-C_6H_4
5f: R^2 = 2-Cl-3-Cl-C_6H_3
5g: R^2 = ^{i}Pr
5h: R^2 = 2-F-C_6H_4
5i: R^2 = 4-F-C_6H_4
5j: R^2 = 4-MeO-C_6H_4

Scheme 1 Reagents and conditions: (A) anisole, anhydrous $AlCl_3$, 0–5°C, acetone; (B) morpholine, acetone, $NaHCO_3$, 35–40°C; (C) arylamine, DMF, $NaHCO_3$, 80–90°C; (D) piperazine derivative, DMF, $NaHCO_3$, 80–90°C.

characterized by IR and NMR and purity was established with elemental analysis.

Antimicrobial activity

The antimicrobial screening was performed for all synthesized *s*-triazine derivatives. Compounds were evaluated *in vitro* for their biological efficacy against Gram positive and Gram negative bacteria (*Klebsiella pneumoniae* MTCC 109, *Pseudomonas aeruginosa* MTCC 741, *Staphylococcus aureus* MTCC 96, *Bacillus cereus* MTCC 619) and fungi (*Candida albicans* MTCC 183 and *Aspergillus niger* MTCC 282) using a broth dilution technique. Ciproflaxin (an antibacterial antibiotic) and ketoconazole (an antifungal antibiotic) were used at a concentration of 3.1 μg/mL as reference drugs. Several compounds were found to be active at a similar concentration level against particular bacteria and fungi. Whereas none of the compounds show activity at this concentration against *K. pneumonia* or *P. aeruginosa*, agents **4e** and **5d** show comparable activity against *B. cereus* and *S. aureus*, respectively. Compound **4g** is active against fungi *C. albicans*, and two compounds **4i** and **5i** show activity at this concentration against *A. niger*.

Experimental

General

Melting points were recorded using an open capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra (400 MHz) were recorded in DMSO-d_6 on a Bruker WM 400 instrument. IR spectra were recorded in KBr pellets on a Shimadzu FTIR spectrophotometer. Elemental analyses were carried out on a Carlo Erba-1108 elemental analyzer. The purity of all synthesized compounds was checked using thin layer chromatography (TLC) on silica gel-coated sheets (Merck Kiesel 60 GF-254, 0.2 mm thickness).

Synthesis of 2,4-dichloro-6-(4-methoxyphenyl)-1,3,5-triazine (2)

A stirred solution of cyanuric chloride (**1**, 0.108 mol, 20 g) and anisole (0.108 mol, 11.8 g) in acetone (50 mL) was treated portion-wise with $AlCl_3$ (0.108 mol, 14.4 g) at 0–5°C for 2 h. The mixture was stirred for an additional 15 h at room temperature. The progress of reaction was monitored by TLC using hexane/ethyl acetate (3:2) as an eluent. After completion of the reaction the mixture was treated with 50% HCl. The solid product obtained was filtered, washed with water, dried, and crystallized from acetone: yield 55%; IR: 1250, 3070 cm^{-1}; ^{1}H NMR: δ 3.85 (s, 3H), 7.10 (m, 2H), 7.90 (m, 2H); mp 132–136°C (dec). (Lit. mp 133–136°C [21].)

Synthesis of 2-chloro-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine (3)

Morpholine (0.195 mol, 17.0 g) in acetone (50 mL) was slowly added to a well-stirred slurry of compound **2** (0.195 mol, 50 g) and $NaHCO_3$ (18 g, 0.215 mol) in acetone (50 mL) at a controlled temperature of 35–40°C. The reaction mixture was stirred for 6 h. The progress of reaction was monitored by TLC using acetone/toluene (4:1) as an eluent. After completion of the reaction, the solution was poured onto crushed ice. The solid product obtained was filtered, dried, and recrystallized from acetone: yield 60% yield; mp 70–75°C (dec); IR: 1251, 1315, 3067, 844 cm^{-1}; ^1H NMR: δ 3.80 (s, 3H), 3.59–3.63 (t, J = 5.2 Hz), 3.87 (t, 4H, J = 5.2 Hz), 7.10 (m, 2H), 7.90 (m, 2H).

Synthesis of compounds 4a–i

An aniline (53.7 mmol) in dimethylformamide (DMF, 50 mL) was allowed to react with compound **3** (16.5 g, 53.7 mmol) in DMF (50 mL) in the presence of $NaHCO_3$ (4.96 g, 59.1 mmol) at 80–90°C for 5–10 h. The progress of reaction was monitored by TLC using hexane/ethyl acetate (4:1) as eluent. After completion of the reaction, the mixture was poured onto crushed ice. The solid product thus obtained was filtered, dried, and crystallized from methanol.

4-(4-Methoxyphenyl)-6-morpholino-*N*-phenyl-1,3,5-triazine-2-amine (4a) This compound was obtained in 70% yield; mp 114–116°C (dec); IR: 3279, 1246, 1325, 3085, 836 cm^{-1}. ^1H NMR: δ 3.25 (s, 3H), 3.65 (m, 4H), 6.0 (s, 1H), 3.82 (m, 4H), 6.85 (m, 9H). Anal. Calcd for $C_{20}H_{21}N_5O_2$: C, 66.10; H, 5.82; N, 19.27. Found: C, 66.14; H, 5.85; N, 19.21.

4-(4-Methoxyphenyl)-6-morpholino-*N*-(3-nitrophenyl)-1,3,5-triazine-2-amine (4b) This compound was obtained in 65% yield; mp 120–124°C (dec); IR: (cm^{-1}): 3285, 1211, 1315, 3067, 844 cm^{-1}; ^1H NMR: δ 3.22 (s, 3H), 3.61 (m, 4H), 6.07 (s, 1H), 3.87 (m, 4H), 7.90 (m, 8H). Anal. Calcd for $C_{20}H_{20}N_6O_4$: C, 58.82; H, 4.94; N, 20.58. Found: C, 58.89; H, 4.95; N, 20.52.

4-(4-Methoxyphenyl)-6-morpholino-*N*-(4-nitrophenyl)-1,3,5-triazine-2-amine (4c) This compound was obtained in 62% yield; mp 131–133°C (dec); IR: 3276, 1244, 1310, 3061, 849 cm^{-1}; ^1H NMR: δ 3.28 (s, 3H), 3.68 (m, 4H), 6.11 (s, 1H), 3.81 (m, 4H), 6.85 (m, 8H). Anal. Calcd for $C_{20}H_{20}N_6O_4$: C, 58.82; H, 4.94; N, 20.58. Found: C, 58.88; H, 4.96; N, 20.60.

***N*-(2-Chlorophenyl)-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine-2-amine (4d)** This compound was obtained in 58% yield; mp 128–130°C (dec); IR: 3259, 1255, 1323, 3056, 834 cm^{-1}; ^1H NMR: δ 3.24 (s, 3H), 3.69 (m, 4H), 6.01 (s, 1H), 3.82 (m, 4H), 8.04 (m, 8H). Anal. Calcd for $C_{20}H_{20}ClN_5O_2$: C, 60.38; H, 5.07; N, 17.60. Found: C, 60.30; H, 5.13; N, 17.64.

***N*-(3-Chlorophenyl)-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine-2-amine (4e)** This compound was obtained in 64% yield; mp 150–152°C (dec); IR: 3252, 1256, 1329, 3052, 831 cm^{-1}; ^1H NMR: δ 3.28 (s, 3H), 3.64 (m, 4H), 6.21 (s, 1H), 3.87 (m, 4H), 6.81–8.03 (m, 8H). Anal. Calcd for $C_{20}H_{20}ClN_5O_2$: C, 60.38; H, 5.07; N, 17.60. Found: C, 60.45; H, 5.13; N, 17.53.

***N*-(4-Chlorophenyl)-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine-2-amine (4f)** This compound was obtained in 62% yield; mp 140–142°C (dec); IR: 3262, 1245, 1333, 3065, 842 cm^{-1}; ^1H NMR: δ 3.23 (s, 3H), 3.62 (m, 4H), 6.26 (s, 1H), 3.88 (m, 4H), 6.87 (m, 8H). Anal. Calcd for $C_{20}H_{20}ClN_5O_2$: C, 60.38; H, 5.07; N, 17.60. Found: C, 60.33; H, 5.03; N, 17.65.

4-(4-Methoxyphenyl)-6-morpholino-*N*-(*o*-tolyl)-1,3,5-triazine-2-amine (4g) This compound was obtained in 56% yield; mp 137–139°C (dec); IR: 3255, 1239, 1339, 3045, 855 cm^{-1}; ^1H NMR: δ 3.25 (s, 3H), 2.24 (s, 3H), 3.66 (m, 4H), 6.24 (s, 1H), 3.83 (m, 4H), 6.87–7.98 (m, 8H). Anal. Calcd for $C_{21}H_{23}N_5O_2$: C, 66.83; H, 6.14; N, 18.55. Found: C, 66.87; H, 6.12; N, 18.50.

4-(4-Methoxyphenyl)-6-morpholino-*N*-(*m*-tolyl)-1,3,5-triazine-2-amine (4h) This compound was obtained in 58% yield; mp 122–126°C (dec); IR: 3251, 1259, 1359, 3041, 825 cm^{-1}; ^1H NMR: δ 3.22 (s, 3H), 2.26 (s, 3H), 3.68 (m, 4H), 6.22 (s, 1H), 3.81 (m, 4H), 7.01–8.18 (m, 8H). Anal. Calcd for $C_{21}H_{23}N_5O_2$: C, 66.83; H, 6.14; N, 18.55. Found: C, 66.80; H, 6.15; N, 18.57.

4-(4-Methoxyphenyl)-6-morpholino-*N*-(*p*-tolyl)-1,3,5-triazine-2-amine (4i) This compound was obtained in 63% yield; mp 129–131°C (dec); IR: 3239, 1270, 1328, 3027, 843 cm^{-1}; ^1H NMR: δ 3.25 (s, 3H), 2.29 (s, 3H), 3.64 (m, 4H), 6.15 (s, 1H), 3.84 (m, 4H), 7.14–8.10 (m, 8H); mp 129–131°C (dec). Anal. Calcd for $C_{21}H_{23}N_5O_2$: C, 66.83; H, 6.14; N, 18.55. Found: C, 66.88; H, 6.19; N, 18.60.

Synthesis of compounds 5a–j

Compound **3** (18.45 g, 60.14 mmol) in DMF (50 mL) was allowed to react with a piperazine (60.14 mmol) in the presence of $NaHCO_3$ (5.56 g, 66.15 mmol) at 80–90°C for 5–10 h. The progress of reaction was monitored by TLC using hexane/ethyl acetate (4:1) as an eluent. After completion of the reaction, the mixture was poured onto crushed ice, and the resultant precipitate was filtered, dried, and crystallized from tetrahydrofuran (THF).

2-(4-Methoxyphenyl)-4-morpholino-6-piperazino-1,3,5-triazine (5a) This compound was obtained in 64% yield; mp 178–180°C (dec); IR: 3239, 1279, 1321, 3029, 849 cm^{-1}; ^1H NMR: δ 3.25 (s, 3H), 3.31 (m, 4H), 3.63 (m, 4H), 3.79 (m, 4H), 4.15 (s, 1H), 3.84 (m, 4H), 6.84–7.30 (m, 4H). Anal. Calcd for $C_{18}H_{24}N_6O_2$: C, 60.66; H, 6.79; N, 23.58. Found: C, 60.68; H, 6.80; N, 23.60.

2-(4-Methoxyphenyl)-4-(4-methylpiperazino)-6-morpholino-1,3,5-triazine (5b) This compound was obtained in 68% yield; mp 184–186°C (dec); IR: 3231, 1272, 1325, 3047, 863 cm^{-1}; ^1H NMR: δ 3.27 (s, 3H), 3.32 (m, 4H), 3.69 (m, 4H), 3.84 (m, 4H), 3.31 (s, 3H), 3.84 (m, 4H), 6.88–7.36 (m, 4H). Anal. Calcd for $C_{19}H_{26}N_6O_2$: C, 61.60; H, 7.07; N, 22.69. Found: C, 61.61; H, 7.05; N, 22.73.

2-(4-Ethylpiperazino)-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine (5c) This compound was obtained in 69% yield; mp 166–168°C (dec); IR: 3255, 1265, 1329, 3024, 844 cm^{-1}; ^1H NMR: δ 3.22 (s, 3H), 3.36–3.40 (m, 4H), 3.68 (m, 4H), 3.77 (m, 4H), 1.92 (t, 3H), 2.94 (q, 2H), 3.89 (m, 4H), 6.94–7.38 (m, 4H). Anal. Calcd for $C_{20}H_{28}N_6O_2$: C, 62.48; H, 7.34; N, 21.86. Found: C, 62.46; H, 7.38; N, 21.84.

2-(4-Acetoxypiperazino)-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine (5d) This compound was obtained in 55% yield; mp 170–172°C (dec); IR: 3240, 1270, 1358, 3077, 821 cm^{-1}; ^1H NMR: δ 3.22 (s, 3H), 3.35 (m, 4H), 3.63 (m, 4H), 3.93 (s, 3H), 3.74 (m, 4H), 3.88 (m, 4H), 6.86–7.39 (m, 4H). Anal. Calcd for $C_{20}H_{26}N_6O_4$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.97; H, 6.30; N, 20.32.

2-(3-Chlorophenylpiperazino)-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine (5e) This compound was obtained in 60% yield. IR (KBr, cm^{-1}): 3248 (NH), 1272 (C-O-C), 1355 (CN), 3059, 831. ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 3.25 (s, 3H, Ar-OCH_3), 3.32–3.36 (m, 4H, piperazine), 3.59–3.63 (m, 4H, piperazine), 3.70–3.74 (m, 4H, morpholine), 3.85–3.89 (m, 4H, morpholine), 6.84–7.39 (m, 8H, Ar-H), mp 160–163°C (dec). Anal. Calcd for $C_{24}H_{27}ClN_6O_2$: C, 61.73; H, 5.83; N, 18.00. Found: C, 61.76; H, 5.86; N, 18.05.

2-(2,3-Dichlorophenylpiperazino)-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine (5f) This compound was obtained in 58% yield; mp 179–181°C (dec); IR: 3240, 1279, 1351, 3051, 841 cm^{-1}; ^1H NMR: δ 3.24 (s, 3H), 3.37 (m, 4H), 3.67 (m, 4H), 3.74 (m, 4H), 3.87 (m, 4H), 6.94–7.49 (m, 7H). Anal. Calcd for $C_{24}H_{26}Cl_2N_6O_2$: C, 57.49; H, 5.23; N, 16.76. Found: C, 57.23; H, 5.25; N, 16.73.

2-(4-Isopropylpiperazino)-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine (5g) This compound was obtained in 67% yield; mp 180–182°C (dec); IR: 3230, 1266, 1344, 3065, 843 cm^{-1}; ^1H NMR: δ 3.22 (s, 3H), 3.32 (m, 4H), 3.66 (m, 4H), 2.86 (m, 1H), 2.02 (d, 6H, J = 6.5 Hz), 3.71 (m, 4H), 3.82 (m, 4H), 7.12–7.59 (m, 4H). Anal. Calcd for $C_{21}H_{30}N_6O_2$: C, 63.29; H, 7.59; N, 21.09. Found: C, 63.28; H, 7.58; N, 21.08.

2-[4-(2-Fluorophenyl)piperazino]-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine (5h) This compound was obtained in 67% yield; mp 180–182°C (dec); IR: 3242, 1287, 1361, 3058, 848 cm^{-1}; ^1H NMR: δ 3.21 (s, 3H), 3.34 (m, 4H), 3.65 (m, 4H), 3.72 (m, 4H), 3.86 (m, 4H), 6.98 (m, 8H). Anal. Calcd for $C_{24}H_{27}FN_6O_2$: C, 63.98; H, 6.04; N, 18.65. Found: C, 63.97; H, 6.03; N, 18.63.

2-(4-Fluorophenylpiperazino)-4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine (5i) This compound was obtained in 79% yield; mp 202–205°C (dec); IR: 3248, 1282, 1368, 3052, 841 cm^{-1}; ^1H NMR: δ 3.26 (s, 3H), 3.38 (m, 4H), 3.61 (m, 4H), 3.76 (m, 4H), 3.82 (m, 4H), 7.07–7.79 (m, 8H). Anal. Calcd for $C_{24}H_{27}FN_6O_2$: C, 63.98; H, 6.04; N, 18.65. Found: C, 63.97; H, 6.03; N, 18.63.

2-(4-Methoxyphenyl)-4-(4-methoxyphenylpiperazino)-6-morpholino-1,3,5-triazine (5j) This compound was obtained in 66% yield; mp 192–198°C (dec); IR: 3245, 1284, 1364, 3055, 844 cm^{-1}; ^1H NMR: δ 3.21 (s, 3H), 3.32 (m, 4H), 3.67 (m, 4H), 3.71 (m, 4H), 3.86 (m, 4H), 3.39 (s, 3H), 7.12–7.76 (m, 8H). Anal. Calcd for $C_{25}H_{30}N_6O_3$: C, 64.92; H, 6.54; N, 18.17. Found: C, 64.90; H, 6.53; N, 18.16.

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