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Research Article

Synthesis, Characterization, and Antimicrobial Studies of Novel Series of 2,4-*Bis*(hydrazino)-6-substituted-1,3,5-triazine and Their Schiff Base Derivatives

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The present work represents the synthesis, characterization, and antimicrobial studies of novel series of 2,4-*bis*(hydrazino)-6-substituted-1,3,5-triazine and their Schiff base derivatives. IR, NMR (^{1}H and ^{13}C), elemental analysis, and LC-MS characterized the prepared compounds. The biological activity of the target products was evaluated as well. Twenty-two of the prepared compounds were selected according to their solubility in aqueous DMSO. Only eight compounds showed good activity against the selected pathogenic bacteria and did not show antagonistic effect against fungus *Candida albicans*. Two compounds **4k** and **5g** have wide-range effect presently in Gram-positive and Gram-negative bacteria while other compounds (**4f**, **4i**, **4m**, **5d**, **6i**, and **6h**) showed specific effect against the Gram-negative or Gram-positive bacteria. The minimum inhibitory concentration (MIC, μg/mL) of **4f**, **4i**, **4k**, and **6h** compounds against *Streptococcus mutans* was 62.5 μg/mL, 100 μg/mL, 31.25 μg/mL, and 31.25 μg/mL, respectively. The MIC of **4m**, **4k**, **5d**, **5g,** and **6h** compounds against *Staphylococcus aureus* was 62.5 μg/mL, 31.25 μg/mL, 31.25 μg/mL, 100 μg/mL, and 62.5 μg/mL, respectively. The MIC of **4k**, **5g**, and **6i** compounds against *Salmonella typhimurium* was 31.25 μg/mL, 100 μg/mL, and 62.5 μg/mL, respectively. The MIC of **6i** compound against *Escherichia coli* was 62.5 μg/mL.

1. Introduction

Hydrazones are considered as extraordinary class of compounds in the Schiff bases family, characterized by the presence of -C=N-N-. The two connected nitrogen atoms are unlike nature and the C-N double bond that is conjugated with a lone pair of the terminal nitrogen atom is mainly responsible for their physical and chemical properties [1–7]. This class of compounds is usually used as polydentate chelating agents that can form a variety of complexes with a range of transition and inner transition metals which have attracted the attention of many researchers [8, 9]. Huge derivatives of hydrazones and their metal complexes have been studied and used in different applications, such as metal ions extraction and microdetermination of metal ion [10, 11]. In addition, they have different biological activity, for example, antimicrobial activity [12–14], antifungal activity [15, 16], antitumor activity [17, 18], and insecticides [19].

On the other hand, the growing interest in s-triazine derivatives specially its chlorinated derivative (cyanuric chloride) and its efficient reaction with hydrazine to render mono-, di-, or tri- substituted hydrazino derivatives has increased [20–22]. Several prepared and well explored hydrazino-s-triazine derivatives were reported and considered with special interest in coordination chemistry and supramolecular chemistry [23, 24] as well as their enormous potential in the field of material chemistry [25, 26], complexation with large metal ions [27–36], and pharmaceutical industry [37–43].

In view of this, the present work represents the synthesis and characterization of novel series of Schiff base derived from 2,4-bis(hydrazino)-6-substituted-s-triazine and their antibacterial and antifungal activity.

2. Experimental Section

2.1. Chemistry

2.1.1. Materials. The solvents used were of analytical reagent grade. NMR (^{1}H and ^{13}C) spectra were recorded on a JEOL 400, 600 MHz spectrometer at room temperature. The chemical shifts were measured using internal standard δ = 0 ppm. Elemental analyses were performed on Perkin-Elmer 2400 elemental analyzer, and the values found were within ±0.3% of the theoretical values. Melting points were recorded on a Mel-Temp apparatus in an open capillary and are uncorrected. Fourier transform infrared spectroscopy (FTIR) spectra were recorded on Nicolet 560 spectrometer from KBr discs. The reaction was followed up and the purity was checked using TLC (silica gel-protected aluminum sheets type 60 GF254, Merck). 2-(4-Iodophenyl)-3-(4-nitrophenyl)-5-phenyltetrazolium chloride (INT) (2 mg/mL) was purchased from Sigma and used for the bacterial growth test.

*2.1.2. General Method for the Synthesis of 2,4-Dihydrazino-6-substituted-1,3,5-triazine Derivatives **3a–e**.* Compounds **3a–e** were prepared according to the reported procedure with some modifications [21, 44, 45]. Hydrazine hydrate (80%) in 20 mL acetonitrile was added to a solution of **2a–e** (20 mmol) in acetonitrile (50 mL) at room temperature. The reaction mixture refluxed for 3 h, and then the excess of hydrazine and solvent was removed under vacuum and the crude white precipitate was filtered off, washed with acetonitrile and ether, and then dried to afford the desired products with high yields and purities. The products were used directly in the next step.

*2.1.3. General Procedure for Synthesis of 2,4-Bis(2-benzylidene-hydrazinyl)-6-substituted-1,3,5-triazine Derivatives **4–8**.* 2,4-Dihydrazino-6-substituted-1,3,5-triazine derivatives **3a–e** (2 mmoles) were added portion-wise to a hot solution of different aldehyde or ketone (4 mmoles) in 30 mL ethanol in the presence of 2-3 drops of acetic acid. The reaction mixture was refluxed for 3-4 hours and the progress of the reaction was followed by TLC using ethyl acetate-hexane 2 : 1. The reaction was left to cool down to room temperature and then the product was filtered and dried.

*(1) N-Benzyl-4,6-bis(2-benzylidenehydrazinyl)-1,3,5-triazine-2-amine (**4a**, Supporting Information, Figure S1 in Supplementary Data)*. Beige solid in yield 95%; mp 150–152°C; IR (KBr, cm^{-1}): 3233 (NH), 1679 (C=N), 1587, 1517 (C=C); ^{1}H NMR (DMSO-d$_6$): δ = 4.52 (d, 2H, J = 6.0 Hz, CH_2NH), 7.18 (t, 1H, J = 7.2 Hz, Ar), 7.27 (t, 2H, J = 8.0 Hz, Ar), 7.30–7.42 (m, 8H, Ar), 7.63 (d, 4H, J = 8.0 Hz, Ar), 8.14 (s, 1H, CH), 11.12 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d$_6$): δ = 43.8, 126.9, 127.6, 128.6, 130.1, 136.8, 140.7, 143.0, 157.9, 164.6 ppm; Anal. Calc. for $C_{24}H_{22}N_8$ (422.50): C, 68.23; H, 5.25; N, 26.52. Found: C, 68.51; H, 5.12; N, 26.37.

*(2) 3,3′-((2,2′-(6-(Benzylamino)-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))diphenol (**4b**, Supporting Information, Figure S2 in Supplementary Data)*. White solid in yield 80%; mp 273–275°C; IR (KBr, cm^{-1}): 3371 (OH), 3304 (NH), 1579 (C=N), 1520, 1388 (C=C); ^{1}H NMR (DMSO-d6): δ = 4.54 (d, 2H, J = 6.4 Hz, CH_2NH), 6.77 (dd, 2H, J^4 = 2.4, J^3 = 8.2 Hz, Ar), 7.04 (d, 2H, J = 8.0 Hz, Ar), 7.08 (s, 2H, Ar), 7.22 (t, 3H, J = 8.0 Hz, Ar), 7.32 (t, 2H, J = 7.6 Hz, Ar), 7.38 (s, 2H, Ar), 8.06 (s, 1H, CH), 9.54 (s, 1H, OH), 10.82 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d$_6$): δ = 43.8, 112.9, 116.8, 118.3, 126.9, 127.6, 128.6, 130.1, 136.8, 140.7, 143.0, 157.9, 164.6, 166.6 ppm; Anal. Calc. for $C_{24}H_{22}N_8O_2$ (454.48): C, 63.43; H, 4.88; N, 24.66. Found: C, 63.21; H, 5.01; N, 24.81.

*(3) N-Benzyl-4,6-bis(2-(3-methoxybenzylidene)hydrazinyl)-1,3,5-triazine-2-amine (**4c**, Supporting Information, Figure S3 in Supplementary Data)*. White solid in yield 97%; mp 173–175°C; IR (KBr, cm^{-1}): 3253 (NH), 1584 (C=N), 1515, 1382 (C=C); ^{1}H NMR (DMSO-d$_6$): δ = 3.80 (d, 6H, J = 3.8 Hz, $2OCH_3$), 4.53 (d, 2H, J = 6.0 Hz, CH_2NH), 6.90 (dd, 2H, J^4 = 2.4, J^3 = 8.4 Hz, Ar), 7.17–7.24 (m, 3H, Ar), 7.28–7.36 (m, 6H, Ar), 7.38 (s, 2H, Ar), 8.10 (s, 1H, CH), 10.90 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d$_6$): δ = 43.8, 55.5, 111.4, 115.4, 119.7, 127.0, 127.6, 128.6, 130.2, 136.9, 140.7, 142.7, 159.9, 164.7, 166.5 (2-HN-C=N-) ppm; Anal. Calc. for $C_{26}H_{26}N_8O_2$ (482.54): C, 64.72; H, 5.43; N, 23.22. Found: C, 64.99; H, 5.68; N, 23.00.

*(4) N-Benzyl-4,6-bis(2-(4-methylbenzylidene)hydrazinyl)-1,3,5-triazine-2-amine (**4d**, Supporting Information, Figure S4 in Supplementary Data)*. Beige solid in yield 97%; mp 153–155°C; IR (KBr, cm^{-1}): 3345 (NH), 1681 (C=N), 1604, 1534 (C=C); ^{1}H NMR (DMSO-d$_6$): δ = 2.33 (s, 6H, $2CH_3$), 4.55 (d, 2H, J = 5.6 Hz, CH_2NH), 7.22 (d, 4H, J = 9.2 Hz, Ar), 7.31 (t, 3H, J = 8.0 Hz, Ar), 7.38 (s, 2H, Ar), 7.56 (d, 4H, J = 8.0 Hz, Ar), 8.13 (s, 1H, CH), 11.05 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d$_6$): δ = 21.4, 43.8, 126.9, 127.1, 127.7, 128.6, 129.8, 132.4, 139.0, 139.5, 142.6, 159.9, 164.7, 166.5 ppm; Anal. Calc. for $C_{26}H_{26}N_8$ (450.54): C, 69.31; H, 5.82; N, 24.87. Found: C, 69.01; H, 5.89; N, 25.00.

*(5) N-Benzyl-4,6-bis(2-(4-methoxybenzylidene)hydrazinyl)-1,3,5-triazine-2-amine (**4e**, Supporting Information, Figure S5 in Supplementary Data)*. White solid in yield 99%; mp 152–154°C; IR (KBr, cm^{-1}): 3346 (NH), 1677 (C=N), 1607, 1509 (C=C); ^{1}H NMR (DMSO-d$_6$): δ = 3.78 (s, 6H, $2OCH_3$), 4.51 (d, 2H, J = 6.8 Hz, CH_2NH), 6.97 (d, 4H, J = 8.0 Hz, Ar), 7.31 (t, 1H, J = 8.0 Hz, Ar), 7.37 (s, 2H, Ar), 7.57 (d, 4H, J = 8.0 Hz, Ar), 8.08 (s, 1H, CH), 10.70 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d$_6$): δ = 43.8, 55.6, 112.9, 114.6, 126.9, 128.0, 128.3, 128.5, 140.8, 142.7, 159.9, 164.7, 166.5, 165.0, 172.6 ppm; Anal. Calc. for $C_{26}H_{26}N_8O_2$ (482.54): C, 64.72; H, 5.43; N, 23.22. Found: C, 64.98; H, 5.65; N, 23.47.

*(6) 3,3′-((2,2′-(6-(Benzylamino)-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))diphenol (**4f**, Supporting Information, Figure S6 in Supplementary Data)*. Beige solid in yield 85%; mp 240–242°C; IR (KBr, cm^{-1}): 3433 (OH), 3251 (NH), 1679 (C=N), 1605, 1503 (C=C); ^{1}H NMR (DMSO-d$_6$): δ = 4.55 (d, 2H, J = 5.6 Hz, CH_2NH), 6.82 (d, 4H,

J = 8.0 Hz, Ar), 7.23 (t, 1H, J = 8.0 Hz, Ar), 7.32 (t, 2H, J = 7.6 Hz, Ar), 7.36 (s, 2H, Ar), 7.52 (d, 4H, J = 8.0 Hz, Ar), 8.08 (s, 1H, CH), 9.91 (s, 1H, OH), 11.0 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 47.5, 112.3, 114.8, 116.1, 126.9, 128.7, 129.1, 136.9, 142.8, 160.5, 166.5 ppm; Anal. Calc. for $C_{24}H_{22}N_8O_2$ (454.48): C, 63.43; H, 4.88; N, 24.66. Found: C, 63.68; H, 4.77; N, 24.91.

*(7) N-Benzyl-4,6-bis(2-(4-bromobenzylidene)hydrazinyl)-1,3,5-triazine-2-amine (**4g**, Supporting Information, Figure S7 in Supplementary Data)*. Beige solid in yield 97%; mp 167–169°C; IR (KBr, cm^{-1}): 3348 (NH), 1680 (C=N), 1608, 1540 (C=C); ^{1}H NMR (DMSO-d_6): δ = 4.55 (d, 2H, J = 6.0 Hz, CH_2NH), 6.76 (d, 4H, J = 7.6 Hz, Ar), 7.12 (s, 4H, Ar), 7.23 (t, 1H, J = 7.2 Hz, Ar), 7.32 (t, 2H, J = 8.0 Hz, Ar), 7.36 (s, 2H, Ar), 8.0 (s, 1H, CH), 11.10 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 43.9, 122.8, 127.1, 127.6, 128.6, 128.7, 132.1, 133.4, 134.5, 140.3, 142.3, 161.2, 164.2 ppm; Anal. Calc. for $C_{24}H_{20}Br_2N_8$ (454.48): C, 49.68; H, 3.47; N, 19.31. Found: C, 49.83; H, 3.61; N, 19.52.

*(8) N-Benzyl-4,6-bis(2-(4-chlorobenzylidene)hydrazinyl)-1,3,5-triazine-2-amine (**4h**, Supporting Information, Figure S8 in Supplementary Data)*. White solid in yield 90%; mp 155–157°C; IR (KBr, cm^{-1}): 3350 (NH), 1676 (C=N), 1610, 1542 (C=C); ^{1}H NMR (DMSO-d_6): δ = 4.53 (d, 2H, J = 6.0 Hz, CH_2NH), 7.21 (t, 1H, J = 7.6 Hz, Ar), 7.31 (t, 2H, J = 7.6 Hz, Ar), 7.36 (s, 2H, Ar), 7.49 (d, 4H, J = 8.0 Hz, Ar), 7.65 (d, 4H, J = 8.0 Hz, Ar), 8.12 (s, 1H, CH), 11.02 (brs, 1H, NH) ppm;^{13}C NMR (DMSO-d_6): δ = 45.2, 122.6, 127.0, 128.4, 129.3, 132.3, 134.5, 141.0, 142.7, 161.0, 164.3. Anal. Calc. for $C_{24}H_{20}Cl_2N_8$ (490.12): C, 58.66; H, 4.10; N, 22.80. Found: C, 58.43; H, 4.32; N, 23.03.

*(9) N-Benzyl-4,6-bis(2-(4-fluorobenzylidene)hydrazinyl)-1,3,5-triazine-2-amine (**4i**, Supporting Information, Figure S9 in Supplementary Data)*. Beige solid in yield 94%; mp 172–174°C; IR (KBr, cm^{-1}): 3356 (NH), 1690 (C=N), 1606, 1504 (C=C); ^{1}H NMR (DMSO-d_6): δ = 4.55 (d, 2H, J = 6.0 Hz, CH_2NH), 7.21–7.35 (m, 7H, Ar), 7.37 (s, 2H, Ar), 7.71 (s, 4H, Ar), 8.15 (s, 1H, CH), 11.10 (brs, 1H, NH) ppm;^{13}C NMR (DMSO-d_6): δ = 43.9, 116.2, 127.1, 127.6, 128.6, 128.9, 131.1, 140.2, 142.5, 160.9, 163.5, 163.9 ppm; Anal. Calc. for $C_{24}H_{20}F_2N_8$ (458.47): C, 62.87; H, 4.40; N, 24.44. Found: C, 62.64; H, 4.55, N, 24.69.

*(10) 4,4′-((2,2′-(6-(Benzylamino)-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))bis(N,N-dimethylaniline) (**4j**, Supporting Information, Figure S10 in Supplementary Data)*. Yellow solid in yield 95%; mp 190-191°C; IR (KBr, cm^{-1}): 3334 (NH), 1681 (C=N), 1605, 1527 (C=C); ^{1}H NMR (DMSO-d_6): δ = 2.96 (d, 12H, J = 9.6 Hz, 2N(CH_3)$_2$), 4.55 (d, 2H, J = 6.4 Hz, CH_2NH), 6.73 (d, 4H, J = 7.2 Hz, Ar), 7.22 (t, 1H, J = 7.2 Hz, Ar), 7.31 (t, 2H, J = 7.2 Hz, Ar), 7.37 (s, 2H, Ar), 7.49 (d, 4H, J = 8.0 Hz, Ar), 8.02 (s, 1H, CH), 10.85 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 43.8, 112.2, 122.5, 127.2, 127.5, 128.7, 129.9, 138.2, 151.6, 152.4, 160.5 ppm; Anal. Calc. for $C_{28}H_{32}N_{10}$ (508.62): C, 66.12; H, 6.34; N, 27.54. Found: C, 66.37; H, 6.55; N, 27.67.

*(11) 4,4′-((2,2′-(6-(Benzylamino)-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))bis(benzene-1,2-diol) (**4k**, Supporting Information, Figure S11 in Supplementary Data)*. Beige solid in yield 99%; mp 200–202°C; IR (KBr, cm^{-1}): 3385 (OH), 3341 (NH), 1681 (C=N), 1615, 1513 (C=C); ^{1}H NMR (DMSO-d_6): δ = 4.53 (d, 2H, J = 5.6 Hz, CH_2NH), 7.21 (t, 1H, J = 8.0 Hz, Ar), 7.31 (t, 2H, J = 7.6 Hz, Ar), 7.37 (s, 2H, Ar), 7.55–7.66 (m, 6H, Ar), 8.11 (s, 1H, CH), 9.50 (s, 1H, OH), 10.85 (brs, 1H, NH) ppm;^{13}C NMR (DMSO-d_6): δ = 43.9, 114.3, 116.1, 120.1, 122.3, 127.2, 127.7, 128.7, 140.0, 146.0, 147.8, 149.3, 160.9, 172.5 ppm; Anal. Calc for $C_{24}H_{22}N_8O_4$ (486.48): C, 59.25; H, 4.56; N, 23.03. Found: C, 59.02; H, 4.66; N, 23.25.

*(12) N-Benzyl-4,6-bis(2-(1-(p-tolyl)ethylidene)hydrazinyl)-1,3,5-triazine-2-amine (**4l**, Supporting Information, Figure S12 in Supplementary Data)*. White solid in yield 87%; mp 103–105°C; IR (KBr, cm^{-1}): 3335 (NH), 1691 (C=N), 1587, 1499 (C=C); ^{1}H NMR (DMSO-d_6): δ = 2.26 (s, 6H, 2CH_3), 2.32 (s, 6H, 2CH_3), 4.56 (d, 2H, J = 6.0 Hz, CH_2NH), 7.19–7.23 (m, 5H, Ar), 7.30 (t, 2H, J = 7.2 Hz, Ar), 7.40 (d, 2H, J =7.6 Hz, Ar), 7.71 (s, 4H, Ar), 9.58 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.0, 21.2, 43.8, 126.4, 126.9, 127.8, 128.5, 129.2, 136.4, 138.4, 140.9, 148.3, 165.5, 166.7 ppm; Anal. Calc. for $C_{28}H_{30}N_8$ (478.59): C, 70.27; H, 6.32; N, 23.41. Found: C, 70.50; H, 6.44; N, 23.67.

*(13) 4,4′-((2,2′-(6-(Benzylamino)-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene))diphenol (**4m**, Supporting Information, Figure S13 in Supplementary Data)*. Beige solid in yield 91%; mp. 260–262°C; IR (KBr, cm^{-1}): 3422 (OH), 3317 (NH), 1673 (C=N), 1608, 1502 (C=C); ^{1}H NMR (DMSO-d_6): δ = 2.23 (s, 6H, 2CH_3), 4.56 (d, 2H, J = 5.6 Hz, CH_2NH), 6.78 (d, 4H, J = 8.8 Hz, Ar), 7.21 (t, 1H, J = 7.2, Ar), 7.30 (t, 2H, J = 7.2, Ar), 7.38 (d, 2H, J = 7.2, Ar), 7.66 (s, 4H, Ar), 9.70 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.1 (2CH_3), 43.9 (CH_2NH), 115.4, 127.1, 127.8, 128.1, 128.6, 129.9, 140.2, 149.3, 158.7, 163.9 ppm; Anal. Calc. for: $C_{26}H_{26}N_8O_2$ (482.54): C, 64.72; H, 5.43; N, 23.22. Found: C, 64.55; H, 5.31; N, 23.00.

*(14) N-Benzyl-4,6-bis(2-benzylidenehydrazinyl)-1,3,5-triazine-2-amine (**5a**, Supporting Information, Figure S14 in Supplementary Data)*. White solid in yield 69%; mp 138–140°C; IR (KBr, cm^{-1}): 3225 (NH), 1675 (C=N), 1588, 1516 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.06 (s, 3H, CH_3N), 4.83 (s, 2H, CH_2N), 7.22–7.46 (m, 11H, Ar), 7.62 (brs, 4H, Ar), 8.01 (s, 1H, CH), 11.20 (brs, 1H, NH) ppm;^{13}C NMR (DMSO-d_6): δ = 34.2, 51.3, 126.9, 127.5, 127.9, 128.9, 129.2, 129.7, 135.4, 138.6, 142.8, 164.6, 165.9 ppm; Anal. Calc. for $C_{25}H_{24}N_8$ (436.51): C, 68.79; H, 5.54; N, 25.67. Found: C, 69.10; H, 5.33; N, 25.98.

*(15) N-Benzyl-N-methyl-4-(2-(4-methylbenzylidene)hydrazinyl)-6-(-2-(4-methylbenzylidene)hydrazinyl)-1,3,5-triazine-2-amine (**5b**, Supporting Information, Figure S15 in Supplementary Data)*. White solid in yield 86%; mp 253–255°C; IR (KBr, cm^{-1}): 3229 (NH), 1608 (C=N), 1553, 1527 (C=C); ^{1}H NMR (DMSO-d_6): δ = 2.33 (s, 6H, 2CH_3), 3.10 (s, 3H, CH_3N), 4.87 (s, 2H, CH_2N), 7.21–7.26 (m, 4H, Ar), 7.31–7.38

(m, 5H, Ar), 7.53 (d, 4H, J = 8.0 Hz, Ar) 8.11 (s, 1H, CH), 11.90 (brs, 1H, NH) ppm;^{13}C NMR (DMSO-d_6): δ = 21.4, 34.1, 51.1, 126.8, 127.4, 128.1, 128.8, 129.8, 132.8, 138.7, 139.1, 142.8, 164.7, 165.9 ppm; Anal. Calc. for $C_{27}H_{28}N_8$ (464.56): C, 69.80; H, 6.08; N, 24.12. Found: C, 70.03; H, 6.33; N, 24.42.

*(16) N-Benzyl-4-(2-(4-methoxybenzylidene)hydrazinyl)-6-(2-(4-methoxy benzylidene)hydrazinyl)-N-methyl-1,3,5-triazine-2-amine (**5c**, Supporting Information, Figure S16 in Supplementary Data)*. Beige solid in yield 58%; mp 245–247°C; IR (KBr, cm^{-1}): 3354 (NH), 1678 (C=N), 1605, 1511 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.13 (s, 3H, CH_3N), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.90 (s, 2H, CH_2N), 6.98 (d, 4H, J = 8.0 Hz, Ar), 7.21–7.27 (m, 1H, Ar), 7.30–7.39 (m, 4H, J = 8.0 Hz, Ar), 7.57 (d, 4H, J = 8.0 Hz, Ar), 8.12 (s, 1H, CH), 10.80 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 34.2, 55.8, 114.7, 127.4, 128.9, 129.6, 132.8, 139.5, 142.8, 164.7, 172.6. Anal. Calc. for $C_{27}H_{28}N_8O_2$ (496.58): C, 65.31; H, 5.68; N, 22.57. Found: C, 65.55; H, 5.81; N, 22.79.

*(17) 4,4′-(2,2′-(6-(Benzyl(methyl)amino)-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene)diphenol (**5d**, Supporting Information, Figure S17 in Supplementary Data)*. Beige solid in yield 63%; mp 216–218°C; IR (KBr, cm^{-1}): 3407 (OH), 3345 (NH), 1680 (C=N), 1599, 1512 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.05 (s, 3H, CH_3N), 4.82 (s, 2H, CH_2N), 6.77 (brs, 4H, Ar), 7.23–7.36 (m, 5H, Ar), 7.44 (s, 4H, Ar), 8.01 (brs, 1H, CH), 9.78 (s, 1H, NH), 10.70 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6): δ = 34.2, 51.3, 116.0, 126.5, 127.5, 127.8, 128.5, 128.9, 138.8, 143.2, 150.3, 159.0, 164.5, 172.5 ppm; Anal. Calc. for $C_{25}H_{24}N_8O_2$ (468.51): C, 64.09; H, 5.16; N, 23.92. Found: C, 64.36; H, 5.00; N, 24.10.

*(18) N-Benzyl-4-(2-(4-bromobenzylidene)hydrazinyl)-6-(2-(4-bromobenzylidene)hydrazinyl)-N-methyl-1,3,5-triazine-2-amine (**5e**, Supporting Information, Figure S18 in Supplementary Data)*. White solid in yield 99%; mp 227–229°C; IR (KBr, cm^{-1}): 3227 (NH), 1548 (C=N), 1524, 1404 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.10 (s, 3H, CH_3N), 4.86 (s, 2H, CH_2N), 7.21–7.26 (m, 1H, Ar), 7.31–7.39 (m, 4H, Ar), 7.59–7.66 (m, 8H, Ar), 8.11 (s, 1H, CH), 11.10 (brs, 1H, NH) ppm;^{13}C NMR (DMSO-d_6): δ = 34.2, 51.2, 122.6, 127.5, 128.0, 128.7, 128.8, 132.2, 134.8, 138.6, 141.5, 164.7, 165.9 ppm; Anal. Calc. for $C_{25}H_{22}Br_2N_8$ (594.30): C, 50.52; H, 3.73; N, 18.85. Found: C, 50.19; H, 3.99; N, 18.61.

*(19) N-Benzyl-4-(2-(4-chlorobenzylidene)hydrazinyl)-6-(2-(4-chlorobenzylidene)hydrazinyl)-N-methyl-1,3,5-triazine-2-amine (**5f**, Supporting Information, Figure S19 in Supplementary Data)*. White solid in yield 82%; mp 225–227°C; IR (KBr, cm^{-1}): 3332 (NH), 1584 (C=N), 1514, 1370 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.10 (s, 3H, CH_3N), 4.87 (s, 2H, CH_2N), 7.21–7.27 (m, 1H, Ar), 7.30–7.38 (m, 4H, Ar), 7.47 (d, 4H, J = 8.0 Hz, Ar), 7.65 (d, 4H, J = 8.0 Hz, Ar), 8.13 (s, 1H, CH), 11.10 (brs, 1H, NH) ppm;^{13}C NMR (DMSO-d_6): δ = 34.2, 51.2, 127.5, 128.0, 128.4, 128.9, 129.3, 133.9, 134.4, 138.6, 141.4, 164.7, 165.9 ppm. Anal. Calc. for $C_{25}H_{22}Cl_2N_8$ (505.41): C, 59.41; H, 4.39; N, 22.17. Found: C, 59.66; H, 4.49; N, 22.00.

*(20) N-Benzyl-4-(2-(4-fluorobenzylidene)hydrazinyl)-6-(2-(4-fluorobenzylidene)hydrazinyl)-N-methyl-1,3,5-triazine-2-amine (**5g**, Supporting Information, Figure S20 in Supplementary Data)*. White solid in yield 69%; mp 210–212°C; IR (KBr, cm^{-1}): 3332 (NH), 1602 (C=N), 1500, 1372 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.10 (s, 3H, CH_3N), 4.87 (s, 2H, CH_2N), 7.21–7.29 (m, 5H, Ar), 7.31–7.38 (m, 4H, Ar), 7.69 (s, 4H, Ar), 8.14 (s, 1H, CH), 11.0 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 34.2, 51.3, 116.2, 127.4, 128.1, 128.8, 128.9, 130.6, 138.7, 141.6, 162.1, 163.8, 164.7, 165.0 ppm. Anal. Calc. for $C_{25}H_{22}F_2N_8$ (472.50): C, 63.55; H, 4.69; N, 23.72. Found: C, 63.87; H, 4.89; N, 23.99.

*(21) N-Benzyl-N-methyl-4-(2-(1-(p-tolyl)ethylidene)hydrazinyl)-6-(2-(1-(p-tolyl)ethylidene)hydrazinyl)-1,3,5-triazine-2-amine (**5h**, Supporting Information, Figure S21 in Supplementary Data)*. White solid in yield 46%; mp 150–152°C; IR (KBr, cm^{-1}): 3353 (NH), 1711 (C=N), 1586, 1494 (C=C); ^{1}H NMR (DMSO-d_6): δ = 2.25 (s, 6H, 2CH_3), 2.32 (s, 6H, 2CH_3), 3.11 (s, 3H, CH_3N), 4.90 (s, 2H, CH_2N), 7.19–7.27 (m, 5H, Ar), 7.31–7.36 (m, 2H, Ar), 7.67–7.75 (m, 8H, Ar), 11.0 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 13.9, 21.2, 34.1, 51.1, 126.3, 127.4, 128.1, 128.8, 129.2, 136.4, 138.4, 138.8, 147.9, 165.5, 166.0 ppm; Anal. Calc. for: $C_{29}H_{32}N_8$ (492.62): C, 70.71; H, 6.55; N, 22.75. Found: C, 70.99; H, 6.76; N, 22.98.

*(22) 4,4′-(2,2′-(6-(Benzyl(methyl)amino)-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene)diphenol (**5i**, Supporting Information, Figure S22 in Supplementary Data)*. Beige solid in yield 89%; mp 205–207°C; IR (KBr, cm^{-1}): 3445 (OH), 3347 (NH), 1674 (C=N), 1597, 1503 (C=C); ^{1}H NMR (DMSO-d_6): δ = 2.25 (s, 6H, 2CH_3), 3.11 (s, 3H, CH_3N), 4.90 (s, 2H, CH_2N), 6.78 (d, 4H, J = 8.0 Hz, Ar), 7.25–7.27 (m, 1H, Ar), 7.30–7.38 (m, 4H, Ar), 7.68 (d, 4H, J = 8.0 Hz, Ar), 9.70 (s, 1H, OH), 11.0 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 21.5, 34.3, 51.3, 115.4, 127.5, 127.8, 128.0, 128.9, 131.1, 140.5, 145.4, 158.7, 166.2, 172.5 ppm; Anal. Calc. for $C_{27}H_{28}N_8O_2$ (496.56): C, 65.31; H, 5.68; N, 22.57. Found: C, 65.63; H, 5.33; N, 22.89.

*(23) 4-(4,6-bis(2-Benzylidenehydrazinyl)-1,3,5-triazine-2-yl)morpholine (**6a**, Supporting Information, Figure S23 in Supplementary Data)*. White solid in yield 88%; mp 273–275°C; IR (KBr, cm^{-1}): 3228 (NH), 1596 (C=N), 1559, 1510 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.66 (d, 4H, J = 4.4 Hz, 2 OCH_2-), 3.78 (s, 4H, 2 NCH_2-), 7.36 (t, 2H, J = 7.2 Hz, Ar), 7.42 (t, 4H, J = 7.2 Hz, Ar), 7.65 (d, 4H, J = 7.6 Hz, Ar), 8.14 (s, 1H, CH), 11.0 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 43.8, 66.5, 126.9, 129.2, 129.6, 135.5, 142.8, 164.8, 165.3 ppm; Anal. Calc. for $C_{21}H_{22}N_8O$ (402.45): C, 62.67; H, 5.51; N, 27.84. Found: C, 62.88; H, 5.71; N, 28.00. (m/z) Calcd: 402.45; LC-MS [M + H]; Found: 403 *(Supporting Information, Figure S24 in Supplementary Data)*.

*(24) 4-(4,6-Bis(2-(4-methylbenzylidene)hydrazinyl)-1,3,5-triazine-2-yl)morpholine (**6b**, Supporting Information, Figure S25 in Supplementary Data)*. White solid in yield 92%; mp 298–300°C; IR (KBr, cm^{-1}): 3225 (NH), 1601 (C=N), 1559, 1503 (C=C); ^{1}H NMR (DMSO-d_6): δ = 2.32 (s, 6H, 2CH_3),

3.64 (brs, 4H, 2 OCH_2-), 3.77 (brs, 4H, 2 NCH_2-), 7.23 (d, 4H, J = 8.4 Hz, Ar), 7.55 (d, 4H, J = 7.2 Hz, Ar), 8.10 (s, 1H, CH), 10.90 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 20.4, 43.4, 66.1, 126.6, 129.4, 132.2, 138.9, 143.3, 164.0 ppm; Anal. Calc. for: $C_{23}H_{26}N_8O$ (430.51): C, 64.17; H, 6.09; N, 26.03. Found: C, 64.00; H, 6.21; N, 26.29.

*(25) 4-(4,6-Bis(2-(4-methoxybenzylidene)hydrazinyl)-1,3,5-triazine-2-yl)morpholine (**6c**, Supporting Information, Figure S26 in Supplementary Data)*. White solid in yield 89%; mp. 253–255°C; IR (KBr, cm^{-1}): 3226 (NH), 1605 (C=N), 1565, 1514 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.65 (brs, 4H, 2 OCH_2-), 3.78 (brs, 4H, 2 NCH_2-), 3.81 (s, 6H, 2OCH_3), 6.98 (d, 4H, J = 8.0 Hz, Ar), 7.58 (d, 4H, J = 8.8 Hz, Ar), 8.10 (s, 1H, CH), 10.80 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 43.3, 55.2, 66.1, 114.2, 127.6, 127.9, 142.3, 160.1, 164.2, 165.0 ppm; Anal. Calc. for $C_{23}H_{26}N_8O_3$ (462.51): C, 59.73; H, 5.67; N, 24.23. Found: C, 59.92; H, 5.80; N, 24.47.

*(26) 4,4′-(2,2′-(6-Morpholino-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene)bis(methanylylidene))diphenol (**6d**, Supporting Information, Figure S27 in Supplementary Data)*. White solid in yield 94%; mp 275–277°C; IR (KBr, cm^{-1}): 3435 (OH), 3349 (NH), 1677 (C=N), 1582, 1509 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.64 (brs, 4H, 2 OCH_2-), 3.76 (s, 4H, 2 NCH_2-), 6.82 (d, 4H, J = 5.2 Hz, Ar), 7.49 (s, 4H, Ar), 8.05 (s, 1H, CH), 9.85 (brs, 1H, OH), 11.16 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 43.0, 66.0, 115.7, 125.8, 128.3, 145.0, 149.9, 159.0, 163.5 ppm; Anal. Calc. for: $C_{21}H_{22}N_8O_3$ (434.45): 58.06; H, 5.10; N, 25.79. Found: C, 58.33; H, 5.31; N, 25.50. (m/z) Calcd: 434.45; LC-MS (M + H); Found: 435.2.

*(27) 4-(4,6-Bis(2-(4-Bromobenzylidene)hydrazinyl)-1,3,5-triazine-2-yl)morpholine (**6e**, Supporting Information, Figure S28 in Supplementary Data)*. White solid in yield 83%; mp. 308–310°C; IR (KBr, cm^{-1}): 3225 (NH), 1593 (C=N), 1561, 1515 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.65 (brs, 4H, 2 OCH_2-), 3.77 (brs, 4H, 2 NCH_2-), 7.58 (m, 8H, Ar), 8.10 (s, 1H, CH), 11.10 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 43.5, 66.0, 122.2, 128.3, 131.8, 134.2, 141.3, 164.2, 164.8 ppm; Anal. Calc. for: $C_{21}H_{20}Br_2N_8O$ (560.24): C, 45.02; H, 3.60; N, 20.00. Found: C, 45.31; H, 3.43; N, 20.28. (m/z) Calcd: 560.24; LC-MS [M + H]; Found: 561.1.

*(28) 4-(4,6-Bis(2-(4-Chlorobenzylidene)hydrazinyl)-1,3,5-triazine-2-yl) (**6f**, Supporting Information, Figure S29 in Supplementary Data)*. White solid in yield 96%; mp. 305–307°C; IR (KBr, cm^{-1}): 3226 (NH), 1596 (C=N), 1563, 1515 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.65 (brs, 4H, 2 OCH_2-), 3.78 (brs, 4H, 2 NCH_2-), 7.48 (d, 4H, J = 8.0 Hz, Ar), 7.66 (d, 4H, J = 8.8 Hz, Ar), 8.12 (s, 1H, CH), 11.10 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d6): δ = 43.3, 66.0, 128.0, 128.8, 133.4, 133.9, 141.1, 164.3, 164.8 ppm; Anal. Calc. for: $C_{21}H_{20}Cl_2N_8O$ (471.34): C, 53.51; H, 4.28; N, 23.77. Found: C, 53.77; H, 4.01; N, 23.56. (m/z) Calcd: 471.34; LC-MS [M + H]; Found: 471.2.

*(29) 4-(4,6-Bis(2-(4-Fluorobenzylidene)hydrazinyl)-1,3,5-triazine-2-yl)morpholine (**6g**, Supporting Information, Figure S30 in Supplementary Data)*. White solid in yield 91%; mp. 301–303°C; IR (KBr, cm^{-1}): 3229 (NH), 1601 (C=N), 1568, 1515 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.65 (brs, 4H, 2 OCH_2-), 3.78 (brs, 4H, 2 NCH_2-), 7.25–7.34 (m, 4H, Ar), 7.69–7.74 (m, 4H, Ar), 8.14 (s, 1H, CH), 11.10 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 43.3, 66.1, 115.8, 128.8, 131.4, 141.4, 161.5, 163.9 ppm; Anal. Calc. for $C_{21}H_{20}F_2N_8O$ (438.43): C, 57.53; H, 4.60; N, 25.56. Found: C, 57.87; H, 4.32; N, 25.23.

*(30) 4-(4,6-Bis(2-(1-(p-Tolyl)ethylidene)hydrazinyl)-1,3,5-triazine-2-yl)morpholine (**6h**, Supporting Information, Figure S31 in Supplementary Data)*. The product was obtained as a yellow solid in yield 92%; mp. 235-236°C; IR (KBr, cm^{-1}): 3358 (NH), 1643 (C=N), 1563, 1442 (C=C); ^{1}H NMR (DMSO-d_6): δ = 2.27 (s, 6H, 2CH_3CN), 2.32 (s, 6H, 2CH_3), δ 3.65 (t, 4H, J = 4.0 Hz, 2 OCH_2-), δ 3.80 (t, 4H, J = 4.4 Hz, 2 NCH_2-), 7.20 (d, 4H, J = 8.0 Hz, Ar), δ 7.72 (d, 4H, J = 7.2 Hz, Ar), δ 11.18 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 13.6, 20.8, 43.3, 66.1, 125.9, 128.8, 135.9, 138.0, 149.9, 165.0 ppm; Anal. Calc. for $C_{25}H_{30}N_8O$ (458.56): C, 65.48; H, 6.59; N, 24.44. Found: C, 65.71; H, 6.33; N, 24.29.

*(31) 4,4′-((2,2′-(6-Morpholino-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene))diphenol (**6i**, Supporting Information, Figure S32 in Supplementary Data)*. White solid in yield 93%; mp. 265–267°C; IR (KBr, cm^{-1}): 3430 (OH), 3360 (NH), 1673 (C=N), 1593, 1503 (C=C); ^{1}H NMR (DMSO-d_6): δ = 2.28 (s, 6H, 2CH_3CN), 3.66 (brs, 4H, 2 OCH_2-), 3.82 (brs, 4H, 2 NCH_2-), 6.80 (d, 4H, J = 8.0 Hz, Ar), 7.69 (d, 4H, J = 8.4 Hz, Ar), 9.80 (brs, 1H, OH), 11.80 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.3, 44.1, 66.4, 115.6, 128.2, 129.0, 152.0, 159.1, 165.5, 172.5 ppm; Anal. Calc. for $C_{23}H_{26}N_8O_3$ (462.50): C, 59.73; H, 5.67; N, 24.23. Found: C, 59.99; H, 5.83; N, 24.51.

*(32) 2,4-Bis(2-benzylidenehydrazinyl)-6-(piperidin-1-yl)-1,3,5-triazine (**7a**, Supporting Information, Figure S33 in Supplementary Data)*. White solid in yield 94%; mp. 247–249°C; IR (KBr, cm^{-1}): 3228 (NH), 1677 (C=N), 1550, 1512 (C=C); ^{1}H NMR (DMSO-d_6): δ = 1.54 (s, 4H, 2CH_2), 1.63 (s, 2H, CH_2), 3.80 (s, 4H, 2CH_2N), 7.43 (brs, 6H, Ar), 7.70 (brs, 4H, Ar), 8.18 (s, 1H, CH), 11.0 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 24.7, 25.9, 44.3, 127.1, 129.2, 129.7, 134.9, 142.5, 165.1 ppm; Anal. Calc. for $C_{22}H_{24}N_8$ (400.49): C, 65.98; H, 6.04; N, 27.98. Found: C, 65.79; H, 6.19; N, 28.14. (m/z) Calcd: 400.49; LC-MS [M + H]; Found: 401 *(Supporting Information, Figure S50 in Supplementary Data)*.

*(33) 2,4-Bis(2-(4-methylbenzylidene)hydrazinyl)-6-(piperidin-1-yl)-1,3,5-triazine (**7b**, Supporting Information, Figure S34 in Supplementary Data)*. White solid in yield 89%; mp. 282–284°C; IR (KBr, cm^{-1}): 3235 (NH), 1673 (C=N), 1567, 1509 (C=C); ^{1}H NMR (DMSO-d_6): δ = 1.58 (s, 4H, 2CH_2), 1.62 (d, 2H, J = 4.4 Hz, CH_2), 2.32 (s, 6H, 2CH_3), 3.78 (s, 4H, 2CH_2N), 7.24 (d, 4H, J = 7.2 Hz, Ar), 7.54 (d, 4H, J = 7.6 Hz, Ar), 8.10 (s, 1H, CH), 10.90 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 20.9, 24.3, 25.5, 43.6, 126.4, 129.3, 132.2, 138.7, 142.4, 164.0 ppm; Anal. Calcd for $C_{24}H_{28}N_8$ (428.53): C, 67.27; H, 6.59; N, 26.15. Found: C, 67.43; H, 6.71; N, 26.38.

*(34) 2,4-Bis(2-(4-methoxybenzylidene)hydrazinyl)-6-(piperidin-1-yl)-1,3,5-triazine (**7c**, Supporting Information, Figure S35 in Supplementary Data)*. White solid in yield 94%; mp. 257–259°C; IR (KBr, cm^{-1}): 3341 (NH), 1665 (C=N), 1570, 1512 (C=C); ^{1}H NMR (DMSO-d_6): δ = 1.52 (s, 4H, $2CH_2$), 1.62 (s, 2H, CH_2), 3.79 (s, 6H, $2OCH_3$), 3.81 (s, 4H, $2CH_2N$), 7.0 (d, 4H, J = 8.8 Hz, Ar), 7.60 (d, 4H, J = 8.0 Hz, Ar), 8.09 (s, 1H, CH), 10.90 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 24.2, 25.4, 43.8, 55.3, 114.2, 126.5, 128.2, 140.8, 160.4, 161.6 ppm.

*(35) 4,4′-((2,2′-(6-(Piperidin-1-yl)-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(methanylylidene))diphenol (**7d**, Supporting Information, Figure S36 in Supplementary Data)*. Beige solid in yield 99%; mp. 331–333°C; IR (KBr, cm^{-1}): 3435 (OH), 3349 (NH), 1677 (C=N), 1590, 1511 (C=C); ^{1}H NMR (DMSO-d_6): δ = 1.54 (s, 4H, $2CH_2$), 1.63 (s, 2H, CH_2), 3.78 (s, 4H, $2CH_2N$), 6.86 (s, 4H, Ar), 7.56 (s, 4H, Ar), 8.09 (s, 1H, CH), 9.80 (s, 1H, OH), 10.30 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 24.6, 25.9, 44.5, 116.2, 125.8, 129.3, 142.7, 159.5, 164.0 ppm; Anal. Calcd for: $C_{22}H_{24}N_8O_2$ (432.48): C, 61.10; H, 5.59; N, 25.91. Found: C, 61.33; H, 5.78; N, 25.72. (m/z) Calcd: 432.48; LC-MS [M + H]; Found: 433 *(Supporting Information, Figure S51 in Supplementary Data)*.

*(36) 2,4-Bis(2-(4-Bromobenzylidene)hydrazinyl)-6-(piperidin-1-yl)-1,3,5-triazine (**7e**, Supporting Information, Figure S37 in Supplementary Data)*. White solid in yield 96%; mp. 288–290°C; IR (KBr, cm^{-1}): 3240 (NH), 1673 (C=N), 1569, 1512 (C=C); ^{1}H NMR (DMSO-d_6): δ = 1.52 (s, 4H, $2CH_2$), 1.63 (d, 2H, J = 4.4 Hz, CH_2), 3.78 (s, 4H, $2CH_2N$), 7.60 (d, 4H, J = 8.0 Hz, Ar), 7.64 (d, 4H, J = 8.0 Hz, Ar), 8.11 (s, 1H, CH), 11.15 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 24.3, 25.5, 43.5, 122.1, 128.2, 131.7, 134.3, 140.9, 164.3 ppm; Anal. Calcd for $C_{22}H_{22}Br_2N_8$ (558.27): C, 47.33; H, 3.97; N, 20.07. Found: C, 47.61; H, 3.77; N, 20.25.

*(37) 2,4-Bis(2-(4-chlorobenzylidene)hydrazinyl)-6-(piperidin-1-yl)-1,3,5-triazine (**7f**, Supporting Information, Figure S38 in Supplementary Data)*. White solid in yield 97%; mp. 293–295°C; IR (KBr, cm^{-1}): 3237 (NH), 1679 (C=N), 1570, 1513 (C=C); ^{1}H NMR (DMSO-d_6): δ = 1.52 (s, 4H, $2CH_2$), 1.62 (d, 2H, J = 4.4 Hz, CH_2), 3.78 (s, 4H, $2CH_2N$), 7.49 (d, 4H, J = 8.0 Hz, Ar), 7.68 (d, 4H, J = 8.4 Hz, Ar), 8.13 (s, 1H, CH), 11.20 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 24.2, 25.5, 43.7, 128.1, 128.8, 132.6, 135.9, 141.3, 160, 164.0 ppm; Anal. Calcd for $C_{22}H_{22}Cl_2N_8$ (469.37): C, 56.30; H, 4.72; N, 23.87. Found: C, 56.55; H, 4.94; N, 24.03. (m/z) Calcd: 469.37; LC-MS [M]; Found: 469 *(Supporting Information, Figure S52 in Supplementary Data)*.

*(38) 2,4-Bis(2-(4-Fluorobenzylidene)hydrazinyl)-6-(piperidin-1-yl)-1,3,5-triazine (**7g**, Supporting Information, Figure S39 in Supplementary Data)*. White solid in yield 95%; mp. 275–277°C; IR (KBr, cm^{-1}): 3358 (NH), 1680 (C=N), 1603, 1501 (C=C); ^{1}H NMR (DMSO-d_6): δ = 1.56 (s, 4H, $2CH_2$), 1.64 (s, 2H, CH_2), 3.82 (s, 4H, $2CH_2N$), 7.32 (brs, 4H, Ar), 7.85 (brs, 4H, Ar), 8.23 (brs, 1H, CH), 12.50 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 24.4, 25.9, 44.7, 116.4, 129.7, 130.8, 144.2, 162.7, 164.2 ppm; Anal. Calcd for $C_{22}H_{22}F_2N_8$ (436.46): C, 60.54; H, 5.08; N, 25.67. Found: C, 60.51; H, 5.23; N, 25.38.

*(39) 2-(Piperidin-1-yl)-4,6-bis(2-(1-(p-tolyl)ethylidene)hydrazinyl)-1,3,5-triazine (**7h**, Supporting Information, Figure S40 in Supplementary Data)*. White solid in yield 91%; mp. 222–224°C; IR (KBr, cm^{-1}): 3356 (NH), 1628 (C=N), 1562, 1437 (C=C); ^{1}H NMR (DMSO-d_6): δ = 1.52 (s, 4H, $2CH_2$), 1.62 (s, 2H, CH_2), 2.28 (s, 6H, $2CH_3CN$), 2.33 (s, 6H, $2CH_3$), 3.81 (s, 4H, $2CH_2N$), 7.19 (d, 4H, J = 8.0 Hz, Ar), 7.71 (d, 4H, J = 8.0 Hz, Ar), 9.70 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 13.9, 21.3, 24.9, 26.0, 43.9, 126.4, 129.3, 136.5, 138.4, 147.9, 164.8, 165.6 ppm; Anal. Calcd for $C_{26}H_{32}N_8$ (456.59): C, 68.39; H, 7.06; N, 24.54. Found: C, 68.65; H, 7.33; N, 24.23.

*(40) 4,4′-((2,2′-(6-(Piperidin-1-yl)-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene))bis(ethan-1-yl-1-ylidene))diphenol (**7i**, Supporting Information, Figure S41 in Supplementary Data)*. Beige solid in yield 85%; mp. 288–290°C; IR (KBr, cm^{-1}): 3440 (OH), 3358 (NH), 1672 (C=N), 1597, 1500 (C=C); 1H NMR (DMSO-d_6): δ = 1.55 (s, 4H, $2CH_2$), 1.64 (s, 2H, CH_2), 2.31 (s, 6H, $2CH_3$), 3.84 (s, 4H, $2CH_2N$), 6.82 (brs, 4H, Ar), 7.70 (brs, 4H, Ar), 9.90 (brs, 2H, OH, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.4, 24.6, 26.0, 44.3, 115.6, 128.2, 131.1, 154.2, 159.1, 160.0 ppm; Anal. Calcd for $C_{24}H_{28}N_8O_2$ (460.53): C, 62.59; H, 6.13; N, 24.33. Found: C, 62.82; H, 6.42; N, 24.61. (m/z) Calcd: 460.53; LC-MS [M + 2H]; Found: 463.2 *(Supporting Information, Figure S42 in Supplementary Data)*.

*(41) 2,4-Bis(2-benzylidenehydrazinyl)-6-methoxy-1,3,5-triazine (**8a**, Supporting Information, Figure S43 in Supplementary Data)*. Beige solid in yield 70%; mp 292–294°C; IR (KBr, cm^{-1}): 3224 (NH), 1620 (C=N), 1586, 1547 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.91 (s, 3H, OCH_3), 7.36–7.47 (m, 6H, Ar), 7.67 (d, 4H, J = 7.2 Hz, Ar), 8.19 (s, 1H, CH), 11.35 (brs, 1H, NH), 11.51 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 54.0, 126.8, 128.8, 129.5, 134.7, 144.5, 161.4, 165.5, 171.0 ppm; Anal. Calcd for $C_{18}H_{17}N_7O$ (347.38): C, 62.24; H, 4.93; N, 28.23. Found: C, 62.51; H, 5.04; N, 28.49.

*(42) 2-Methoxy-4,6-bis(2-(4-methylbenzylidene)hydrazinyl)-1,3,5-triazine (**8b**, Supporting Information, Figure S44 in Supplementary Data)*. White solid in yield 84%; mp 298–300°C; IR (KBr, cm^{-1}): 3323 (NH), 1616 (C=N), 1586, 1540 (C=C); ^{1}H NMR (DMSO-d_6): δ = 2.33 (s, 6H, $2CH_3$), 3.89 (s, 3H, OCH_3), 7.25 (d, 4H, J = 7.2 Hz, Ar), 7.56 (d, 4H, J = 7.2 Hz, Ar), 8.14 (s, 1H, CH), 11.28 (brs, 1H, NH), ppm;^{13}C NMR (DMSO-d_6): δ = 21.5, 54.4, 127.1, 129.8, 132.4, 139.6, 144.3, 165.5, 166.2 ppm; Anal. Calcd for $C_{20}H_{21}N_7O$ (375.44): C, 63.98; H, 5.64; N, 26.12. Found: C, 63.82; H, 5.73; N, 26.33.

*(43) 2-Methoxy-4,6-bis(2-(4-methoxybenzylidene)hydrazinyl)-1,3,5-triazine (**8c**, Supporting Information, Figure S45 in Supplementary Data)*. White solid in yield 86%; mp 300–302°C; IR (KBr, cm^{-1}): 3277 (NH), 1612 (C=N), 1589, 1545 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.79 (s, 6H, $2OCH_3$), 3.89 (s, 3H, OCH_3), 7.0 (d, 4H, J = 8.0 Hz, Ar), 7.61 (d, 4H, J = 7.2 Hz, Ar),

8.13 (s, 1H, CH), 11.22 (brs, 2H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 53.9, 55.3, 114.3, 127.2, 128.2, 144.0, 160.4, 164.7 ppm; Anal. Calcd for $C_{20}H_{21}N_7O_3$ (407.43): C, 58.96; H, 5.20; N, 24.06. Found: C, 58.77; H, 5.02; N, 24.33.

*(44) 4,4′-(2,2′-(6-Methoxy-1,3,5-triazine-2,4-diyl)bis(hydrazin-2-yl-1-ylidene)bis(methanylylidene))diphenol (**8d**, Supporting Information, Figure S46 in Supplementary Data)*. Beige solid in yield 83%; mp 294–296°C; IR (KBr, cm^{-1}): 3522 (OH), 3268 (NH), 1618 (C=N), 1545, 1514 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.84 (s, 3H, OCH_3), 6.77 (d, 4H, J = 8.0 Hz, Ar), 7.45 (d, 4H, J = 7.2 Hz, Ar), 8.03 (s, 1H, CH), 9.83 (s, 1H, OH), 11.10–11.30 (brs, 2H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 53.9, 115.7, 125.8, 128.4, 144.0, 158.9, 165.8, 171.0 ppm; Anal. Calcd for $C_{18}H_{17}N_7O_3$ (379.37): C, 56.99; H, 4.52; N, 25.84. Found: C, 56.76; H, 4.76; N, 26.07.

*(45) 2,4-Bis(2-(4-bromobenzylidene)hydrazinyl)-6-methoxy-1,3,5-triazine (**8e**, Supporting Information, Figure S47 in Supplementary Data)*. White solid in yield 87%; mp. 317–319°C; IR (KBr, cm^{-1}): 3318 (NH), 1678 (C=N), 1586, 1535 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.89 (s, 3H, OCH_3), 7.62 (brs, 8H, Ar), 8.15 (s, 1H, CH), 11.4 (brs, 1H, NH), 11.70 (brs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 54.0, 122.6, 128.5, 131.7, 133.9, 142.8, 163.8 ppm; Anal. Calcd for $C_{18}H_{15}Br_2N_7O$ (505.17): C, 42.80; H, 2.99; N, 19.41. Found: C, 43.01; H, 3.15; N, 19.66.

*(46) 2,4-Bis(2-(4-chlorobenzylidene)hydrazinyl)-6-methoxy-1,3,5-triazine (**8f**, Supporting Information, Figure S48 in Supplementary Data)*. Beige solid in yield 86%; mp 308–310°C; IR (KBr, cm^{-1}): 3315 (NH), 1616 (C=N), 1586, 1534 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.91 (s, 3H, OCH_3), 7.50 (d, 4H, J = 7.2 Hz, Ar), 7.69 (d, 4H, J = 8.0 Hz, Ar), 8.17 (s, 1H, CH), 11.50 (brs, 2H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 53.9, 122.5, 128.4, 128.9, 131.7, 133.9, 141.4, 161.0 ppm; Anal. Calc. for $C_{18}H_{15}Cl_2N_7O$ (416.26): C, 51.94; H, 3.63; N, 23.55. Found: C, 51.86; H, 3.88; N, 23.79.

*(47) 2,4-Bis(2-(4-fluorobenzylidene)hydrazinyl)-6-methoxy-1,3,5-triazine (**8g**, Supporting Information, Figure S49 in Supplementary Data)*. Beige solid in yield 69%; mp 323–325°C; IR (KBr, cm^{-1}): 3217 (NH), 1603 (C=N), 1547, 1504 (C=C); ^{1}H NMR (DMSO-d_6): δ = 3.90 (s, 3H, OCH_3), 7.26–7.30 (m, 4H, Ar), 7.71–7.74 (m, 4H, Ar), 8.17 (s, 1H, CH), 11.40 (brs, 2H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 54.0, 116.0, 128.6, 131.2, 143.2, 161.4, 164.2 ppm; Anal. Calcd for $C_{18}H_{15}F_2N_7O$ (383.35): C, 56.39; H, 3.94; N, 25.58. Found: C, 56.65; H, 4.05; N, 25.32.

2.2. Antimicrobial Activity. The antibacterial activity of the prepared compounds was assessed against two selected bacteria groups: Gram-positive bacteria, namely, *Streptococcus mutans* (wild strain) and *Staphylococcus aureus* (ATCC 29213), and Gram-negative bacteria, namely, *Escherichia coli* (ATTC 25922) *and Salmonella typhimurium* (ATCC 14028), maintained in Brain Heart Infusion medium at −20°C. One mL of each targeted grown bacterial culture was added to 100 mL of Brain Heart Infusion broth and incubated at 37°C ± 1°C for subculture of all targeted bacterial cultures. Using of sterile physiological solution, concentration of bacterial inoculum was determined to be 10^8 CFU/mL (0.5 McFarland turbidity standards) for antimicrobial tests. In case of fungus *Candida albicans*, the PDA was used as a medium in antagonistic activity against the tested fungi.

2.2.1. Primary Screening of Synthetic Organic Compounds for Bioactivity by Agar Diffusion Disc. The tested compounds were dissolved in DMSO and prepared at concentration 2500 μg/mL. The sterilized Mueller Hinton agar plates seeded with pathogenic bacteria were prepared; 6 mm paper discs with 100 μg of the tested compounds were placed in the plates seeded with tested pathogenic bacteria. The inoculated plates were kept at 37°C for 24 h for bacteria while, in case of fungi, the used medium in antagonistic activity against tested fungi is PDA. Antimicrobial activity was determined by the inhibition zone [46].

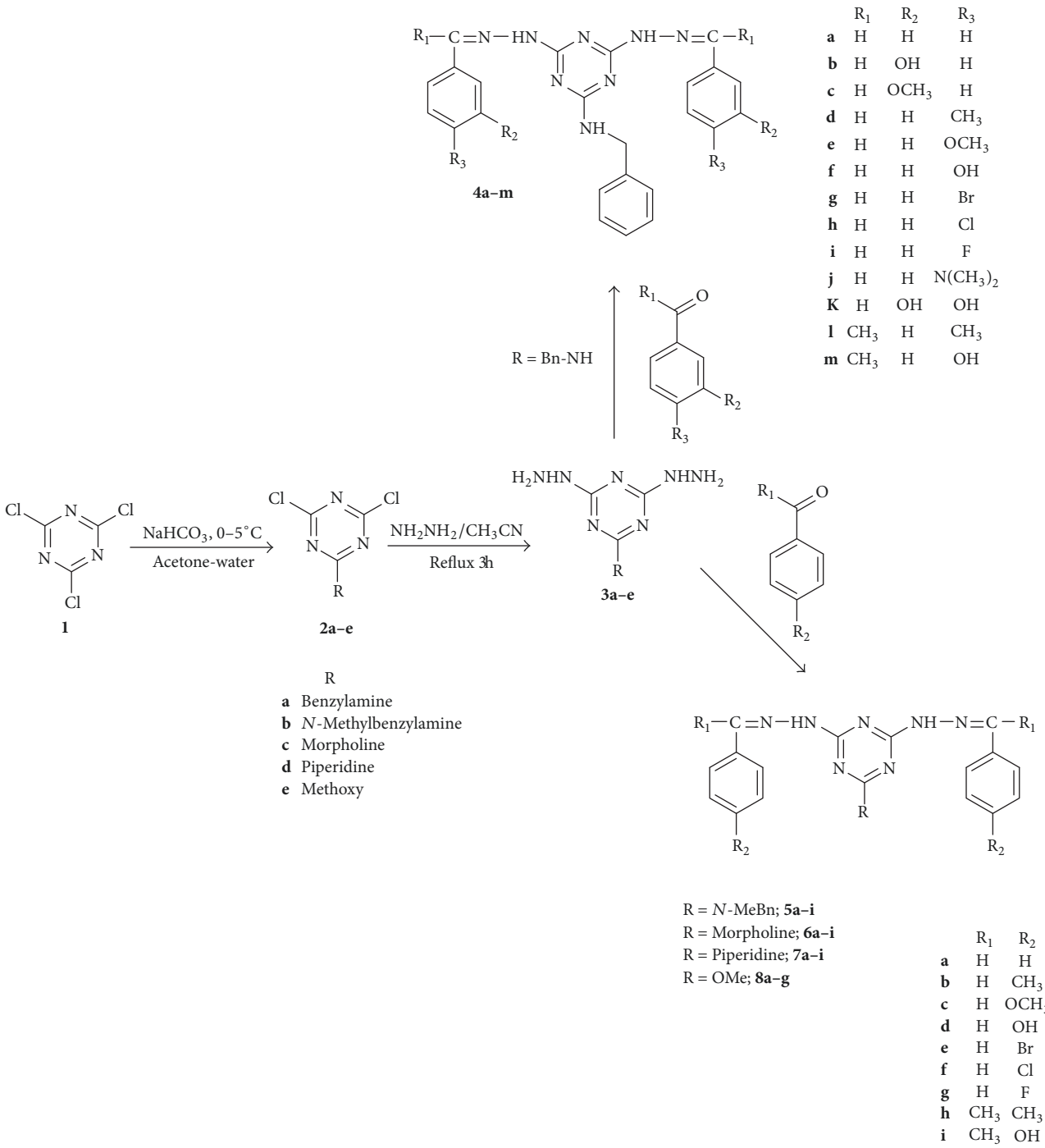
2.2.2. Minimum Inhibitory Concentration (MIC) Determination. The bioactivity of the tested compounds was determined by using a microdilution method, using Mueller–Hinton broth. The inoculum was prepared as described previously and the tested compounds were stocked in 0.25% of DMSO (concentration of each compound 1.25 mg/mL). After that, serial dilutions were done by addition of 100 μL of culture broth which was poured in microplate and 25 μL of each concentration of tested compound in the first line of microplate to reach concentrations ranging from 125 to 0.973 μg/mL in presence of the positive and negative control. The microplates were vaccinated with 5 μL of a bacterial inoculum (10^8 CFU/mL) and were kept for 24 h at 37°C in triplicate tests. After incubation period, we added 20 μL INT (0.5 mg/mL) to achieve bacterial growth. The INT containing microplates were incubated at 37°C for 30 min and the collected data were expressed in micrograms per milliliters [47].

3. Results and Discussion

3.1. Chemistry. The first chlorine atom of cyanuric chloride **1** was replaced by benzylamine, *N*-methylbenzylamine, morpholine, piperidine, or methoxy, while two hydrazine groups replaced the second and third chlorine atoms. Accordingly, 2,4-dihydrazino-6-substituted-1,3,5-triazine derivatives **3a–e** were prepared by displacement of the two chlorine atoms by two hydrazine groups.

Cyanuric chloride **1** was first reacted with different amines such as benzylamine, *N*-methylbenzylamine, morpholine, piperidine, or methanol at 0°C for 1-2 h to afford the products **2a–e** (Scheme 1); the spectral data agreed with the reported data [44, 45]. The dichloro derivatives **2a–e** were reacted with hydrazine hydrate (80%) under reflux using acetonitrile as a solvent to render the products of 2,4-dihydrazino-6-substituted-1,3,5-triazine derivatives **3a–e** which were used directly in the next step without further purification (Scheme 1).

The products **4–8** were prepared by condensation of the hydrazine derivatives **3a–e** with different aldehydes or



	R_1	R_2	R_3
a	H	H	H
b	H	OH	H
c	H	OCH_3	H
d	H	H	CH_3
e	H	H	OCH_3
f	H	H	OH
g	H	H	Br
h	H	H	Cl
i	H	H	F
j	H	H	$N(CH_3)_2$
K	H	OH	OH
l	CH_3	H	CH_3
m	CH_3	H	OH

	R_1	R_2
a	H	H
b	H	CH_3
c	H	OCH_3
d	H	OH
e	H	Br
f	H	Cl
g	H	F
h	CH_3	CH_3
i	CH_3	OH

Scheme 1: Synthesis of 6-substituted-s-triazine-Schiff base derivative.

substituted acetophenone in ethanol as solvent and in the presence of drops of acetic acid (Scheme 1).

The ^{1}H NMR spectrum of **4b** (Figure 1) as a prototype for the **4a–m** series displayed two doublet peaks at δ 4.54 (J = 6.4 Hz) and 7.04 ppm (J = 8.0), attributed to resonances of protons of CH_2N and 2H-6 respectively, doublet of doublet at δ 6.77 ppm which integrated two protons for 2H-4, two triplets at δ 7.22 (J = 8.0 Hz) and 7.32 ppm (J = 7.6) for H-4′, 2H-5, and H-3′, H-5′, and four singlets at δ 7.08, 7.38, 8.06, and 9.54 ppm for 2H-2, H-2′ combined H-6′, CH, and OH, respectively, while the NH proton appeared as abroad singlet at δ 10.82 ppm. The ^{13}C NMR spectrum also reveals the symmetry of **4b**, as indicated by the appearance of fourteen distinct carbon peaks, among which are four peaks at δ 112.9, 116.8, 118.3, 126.9, 127.6, 128.6, 130.1, 136.8, 140.7, and 157.9 ppm related to the aromatic carbons, in addition to four peaks at δ 43.8, 143.0, 164.6, and 166.6 ppm belonging to (CH_2NH), and (C=N), respectively.

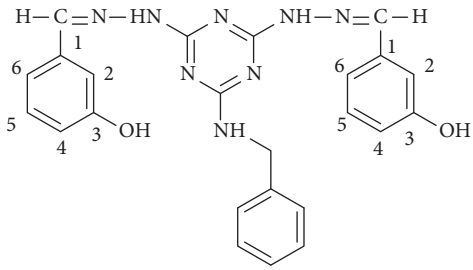


Figure 1: Structure of **4b**.

The ^{1}H NMR spectrum of **5b** as a prototype for the **5a–i** series exhibited three singlets at δ 2.33, 3.10, and 4.87 ppm, which were assigned to protons of $2CH_3$, CH_3N, and CH_2N, respectively. This spectrum showed three signals for aromatic rings at δ 7.21–7.26 (m, 4H, 2H-3, and 2H-5), 7.31–7.38 (m, 5H, H-2′, H-3′, H-4′, H-5′, and H-6′), and 7.53 (d, 4H, J = 8.0 Hz, 2H-2, and 2H-6) ppm. This spectrum also showed a sharp singlet at δ 8.11 ppm integrating one proton, which was assigned to CH, in addition the broad singlet at δ 11.90 ppm for NH. The ^{13}C NMR spectrum of **5b** showed fourteen individual carbon signals. The three signals in the sp^3 region appeared at δ 21.4, 34.1, and 51.1 ppm for ($2CH_3$), (CH_3N), and (CH_2N), respectively, in addition to signals at δ142.8, 164.7, and 165.9 ppm for (C=N). Assignments of resonances of six carbons of the benzyl were at δ127.4, 128.1, 128.8, and 138.7 ppm. The signals of the remaining aromatic carbons appeared at δ126.8, 129.8, 132.8, and 139.1 ppm.

The ^{1}H NMR spectrum of **6a** as a prototype for the **6a–i** series showed two sharp singlets at δ 3.66 and 3.78 ppm for 2 OCH_2- and 2 NCH_2- related to the morpholine, respectively, singlet at δ 8.14 ppm for CH, and a broad singlet at δ 11.0 for NH. Three signals for aromatic protons appeared at δ 7.42 (t, 4H, J = 7.2 Hz, 2H-3, and 2H-5) and 7.65 (d, 4H, J = 7.6 Hz, 2H-2, and 2H-6). The ^{13}C NMR spectrum also confirms the structure for compound **6a**, as indicated by the appearance of two signals at δ 43.8 and 66.5 ppm for (2 NCH_2-) and (2 OCH_2-), respectively, for the morpholino moiety, while the other three signals appeared at δ142.8, 164.8, and 165.3 ppm for (C=N), in addition to the observation of the aromatic ring carbons appearing at δ126.9, 129.2, 129.6, and 135.5 ppm, respectively. The LC-MS of compound **6a** (Supporting Information, Figure S24 in Supplementary Data) the exact molecular mass [M + H] 403 (m/z calcd. 402.45) with R_t 15.3 min, using buffer A: 0.1% formic acid in H_2O; and buffer B: 0.1% formic acid in CH_3CN in 30 min.

The ^{1}H NMR spectrum of **7i** as a prototype for **7a–i** series showed three singlet peaks at δ 1.55, 1.64, and 3.84 ppm for the $2CH_2$, CH_2, and $2NCH_2$ (piperidine moiety), while it showed a singlet at δ 2.31 ppm for the methyl group of the acetophenone moiety and two broad singlets at δ 9.90 and 11.0 ppm for OH and NH, respectively, beside two doublets forming AB system at δ 6.82 (J = 8.0 Hz) and 7.70 ppm (J = 7.2 Hz) for the aromatic proton H-3, H-5 and H-2, H-6, respectively. The ^{13}C NMR spectrum of **7i** exhibited absorption peak at δ 14.4 related to methyl group, three peaks for the piperidine residue at δ 24.6, 26.0, and 44.3 ppm related to (CH_2), ($2CH_2$), and ($2CH_2N$), respectively, and absorption peaks at δ 154.2 and 160.0 ppm related to (C=N), besides four peaks at δ115.6, 128.2, 131.1, and 159.1 ppm for the aromatic carbons. The LC-MS of compound **7i** (Supporting Information, Figure S42 in Supplementary Data) using buffer A: 0.1% formic acid in H_2O and buffer B: 0.1% formic acid in CH_3CN in 30 min showed one peak at R_t 14.08 min with the expected mass [M + 2H] 463.2 (m/z calcd. 460.53).

The ^{1}H NMR spectrum of **8b** as a prototype for the **8a–g** series revealed the resonances of protons methyl group at δ 2.33 ppm (s, $2CH_3$) and methoxy group at δ 3.89 ppm (s, OCH_3), in addition to the two doublets that appeared at δ 7.25 (d, 4H, J = 7.2 Hz) and 7.56 ppm (d, 4H, J = 7.2 Hz) representing of 2H-2, 2H-3, and 2H-5, 2H-6 (AB system) while singlet (integrated for one proton) appearing at δ 8.14 ppm was attributed to CH. Finally, the proton of NH group appeared as broad singlet at δ 11.28 ppm. The ^{13}C NMR spectrum of **8b** showed signal at δ 21.5 for the methyl carbon while methoxy carbon appeared at δ 54.4 ppm and the aromatic carbons signals at δ 127.1, 129.8, 132.4, and 139.6 ppm. The three signals at δ144.3, 165.5, and 166.2 ppm in the later spectrum were assigned to (C=N).

3.2. Biology

3.2.1. Bioactivity of Tested Compounds against the Pathogenic Bacteria and Fungus Candida albicans. In the present study, twenty-two compounds from the above series **4–8** were tested for bioactivities against the selected bacteria and fungi; only eight compounds have antiactivities of target pathogenic bacteria. The results in Table 1 showed that the tested compounds, namely, **4f, 4k, 4l, 4m, 5d, 5g, 6i,** and **6h,** have bioactivity against the target pathogenic bacteria as antimicrobial agents and do not have antagonistic effect against fungus *Candida albicans*. The present study also showed that compounds **4k** and **5g** have wide-range effect presently in Gram-positive and Gram-negative bacteria, while compounds **6i** and **6h** were specific in the effect against the Gram-negative and Gram-positive bacteria, respectively. Table 1 also showed that compounds **4f** and **4l** showed activity against *Streptococcus mutans,* while compounds **4m** and **5d** showed activity against *Staphylococcus aureus.*

A lowest concentration of chemical compound that inhibits the bacterial growth is the minimum inhibitory concentration (MIC, μg/mL). The MIC of compound **4k** that inhibited all the tested pathogenic bacteria was 31.25 μg/mL, while the MIC of compound **4f** that inhibited the *Streptococcus mutans* was 62.5 μg/mL, the MIC of compound **4l** that inhibited *Streptococcus mutans* was 100 μg/mL, and the MIC of compound **4m** that inhibited *Staphylococcus aureus* was 62.50 μg/mL. The MIC of compound **5d** that inhibited *Staphylococcus aureus* was 31.25 μg/mL, the MIC of compound **5g** that inhibited *Staphylococcus aureus* and *Salmonella typhimurium* was 100 μg/mL, the MIC of compound **6i** that inhibited *Escherichia coli and Salmonella typhimurium* was 62.50 μg/mL, and the MIC of compound **6h** that inhibited *Streptococcus mutans* and *Staphylococcus aureus* was 31.25 and 62.50 μg/mL, respectively (Table 2).

Table 1: Bioactivities of the synthetic organic compounds against some pathogenic bacteria and unicellular fungus *Candida albicans* at 100 μg/paper disc (6 mm).

Compd. number	*Streptococcus mutans*	*Staphylococcus aureus*	*Escherichia coli*	*Salmonella typhimurium*	*Candida albicans*
Control	−	−	−	−	−
4k	+	+	+	+	−
4j	−	−	−	−	−
4f	+	−	−	−	−
4e	−	−	−	−	−
4i	−	−	−	−	−
4l	+	−	−	−	−
4m	−	+	−	−	−
5c	−	−	−	−	−
5d	−	+	−	−	−
5e	−	−	−	−	−
5f	−	−	−	−	−
5g	−	+	−	+	−
5i	−	−	−	−	−
6d	−	−	−	−	−
6f	−	−	−	−	−
6g	−	−	−	−	−
6i	−	−	+	+	−
6h	+	+	−	−	−
8c	−	−	−	−	−
8d	−	−	−	−	−
8f	−	−	−	−	−
8g	−	−	−	−	−

Table 2: Minimum inhibitory concentration (MIC, μg/mL) of bioactive synthetic compounds against target pathogenic bacteria.

Compd. number	*Streptococcus mutans* wild strain	*Staphylococcus aureus*	*Escherichia coli*	*Salmonella typhimurium*
4k	31.25	31.25	31.25	31.25
4f	62.50	-	-	-
4l	100.00	-	-	-
4m	-	62.50	-	-
5d	-	31.25	-	-
5g	-	100.00	-	100.00
6i	-	-	62.50	62.50
6h	31.25	62.50	-	-

It is obvious from Table 1 that small structural variations in s-triazine ring may induce an effect on antibacterial activity, such as in series of benzyl derivatives (**4** series) and the *N*-methylbenzyl derivatives (**5** series); the benzyl derivatives showed more activity than the *N*-benzyl derivatives. The same was observed when the benzyl was substituted by methoxy (**8** series); the benzyl derivatives showed more activity. Also the substituent effect on the benzylidene moiety has a great effect on the antibacterial activity as shown in case of **4** series and **5** series, and it is interesting to note that in most of the cases the fluorine derivatives showed higher activity than the chlorine and bromine derivatives as in case of **5** series. On the other hand, not all the tested compounds showed any antifungal activity; this observation agreed with the reported data for s-triazine derivatives [48, 49].

4. Conclusion

The present work represents the synthesis, characterization, and biological activity of novel series of the s-triazine *bis*-Schiff base. Only twenty-two compounds from the above series **4a–m, 5a–i, 6a–i, 7a–i,** and **8a–g** were tested against Gram-positive and Gram-negative bacteria according to their solubility in aqueous DMSO. Only eight compounds **4k, 4f, 4l, 4m, 5d, 5g, 6i,** and **6h** showed bioactivity against the target pathogenic bacteria as antimicrobial agents and did not show antagonistic effect against fungus *Candida albicans*. Two compounds **4k** and **5g** have wide-range effect presently in Gram-positive and Gram-negative bacteria, while compounds **6i** and **6h** have specific effect against the Gram-negative and Gram-positive bacteria, respectively.

In addition, compounds **4f** and **4l** showed activity against *Streptococcus mutans* while compounds **4m** and **5d** showed activity against *Staphylococcus aureus*.

It is clear that the substituent in the benzylidene as well as the triazine ring may have great effect on the antimicrobial activity. Further investigation is being run in our lab to get a clear depiction on the mode of action and the relation between the biological activity and substituent effect on the s-triazine moiety.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Figures S1–S52: ^{1}H NMR, ^{13}C NMR, and LC-MS spectra. *(Supplementary Materials)*

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