Synthesis, characterization and antimicrobial activity of some new 4-(4-(2-isonicotinoylhydrazinyl)-6-((aryl)amino)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl) benzenesulfonamides

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Abstract In the present study, we have synthesized some novel 4-(4-(2-isonicotinoylhydrazinyl)-6-((aryl)amino)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonamide derivatives (3a-v) and evaluated their in vitro antimicrobial activity against the representative panel of Gram-positive bacteria [Staphylococcus aureus (MTCC 96), Staphylococcus pyogenes (MTCC 442)], Gram-negative bacteria [Escherichia coli (MTCC 443), Pseudomonas aeruginosa (MTCC 1688)] and fungal strains [Candida albicans (MTCC 227), Aspergillus niger (MTCC 282), Aspergillus clavatus (MTCC 1323)]. Evaluation of antimicrobial activity revealed that compounds 3g, 3h, 3t, and 3v were the most active antibacterial, while compounds 3g and 3h were the most potent antifungal agents. The structures of synthesized compounds (3a-v) were elucidated by IR, NMR spectroscopy and elemental analysis.

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1. Introduction

After years of misuse and overuse of antibiotics, bacteria are becoming antibiotic resistant, therefore recent efforts have been directed toward exploring novel antibacterial agents [16]. In order to overcome this rapid development of drug resistance, new agents should preferably consist of chemical characteristics that clearly differ from those of existing agents. Nowadays the discovery and commercial development of numerous therapeutic agents [12] afford reliably effective treatment for many infectious diseases which had previously caused extensive mortality and morbidity. In this context, substituted s-triazine and benzenesulfonamide derivatives have received considerable attention due to their significant activities like antimicrobial [2,3,8,22,23], antibacterial [11], antifungal [19], antitumor [4,18], anti-inflammatory [17].
anticancer [3,10,15,20], antiprotozoals [21], antimalarials [1,3,14]. Profound medicinal applications associated with isonicotinohydrazide render them as useful structural units in drug research [13].

Due to rapid development of drug resistance, tolerance and side effects there is a fundamental and critical need for the development of a new generation of antimicrobial agents which would exhibit improved pharmacological properties and drug-resistance profiles. Previously, our research group has also reported synthesis, characterization and antimicrobial evaluation of \(N'(4-((arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide \) derivatives [5]. Keeping this in mind we have subsequently carried out the synthesis of s-triazine based isoniazid and benzenesulfonamide derivatives to explore the synthesis of more potential bioactive molecules in one framework.

2. Experimental part

2.1. Materials and physical measurements

The completion of reaction and purity of compounds were checked on aluminum coated TLC plates 60 F245 (E. Merck) using n-hexane:ethyl acetate (7.5:2.5 V/V) as mobile phase and visualized under ultraviolet (UV) light or in an iodine chamber. Melting points were determined on an electro thermal melting point apparatus and were reported uncorrected. Elemental analysis (% C, H, N) was carried out by a Perkin–Elmer 2400 CHN analyzer. IR spectra of all the compounds were recorded on a Perkin–Elmer FT-IR spectrophotometer in KBr. \(^1\)H NMR (300 MHz) and \(^13\)C NMR (100 MHz) spectra were recorded on Bruker spectrometer. In the conventional method, compounds were synthesized using Random synthesizer.

2.2. Preparation of \(N'(4,6,7-trichloro-1,3,5-triazin-2-yl)isonicotinohydrazide \) (1)

A mixture of 2,4,6-trichloro-1,3,5-triazine (0.01 mol) in acetone (15 mL) and isoniazid (0.01 mol) was taken in a conical flask. To this mixture, 4% NaOH was added drop-wise at 0–5 °C temperature. The solution was stirred for 2 h. The reaction mixture was then poured onto crushed ice with constant stirring and neutralized with dil. HCl. The solid obtained was filtered, washed with water, dried and recrystallized from 1,4-dioxane. Yield: 70.0%; m.p.: 235 °C; IR (KBr, \(\upsilon, cm^{-1}\)): 788 (C–Cl, Stretching), 895 (S–N–O, stretching), 1135 (S–O, stretching in SO2), 1392 (N–H, bending), 1640 (C–C, stretching), 1690 (C–O, stretching), 1890 (C–N, stretching), 3035 (C–H, stretching in aromatic), 3445 (N–H, stretching in amine); \(^1\)H NMR (300 MHz, DMSO-d6, \(\delta, ppm\)): 6.54 (2H, Ar–NH–triazine), 6.72 (1H, triazine–NH–NH–), 6.93 (1H, pyrimidine), 7.1–7.83 (4H, Ar–H), 8.03 (1H, –SO2NH–), 8.87 (2H, pyrimidine), 9.78 (2H, pyridine), 3448 (N–H, stretching in amine); \(^13\)C NMR (100 MHz, DMSO-d6, \(\delta, ppm\)): 164.1 (1C, C–NH– attached with arylsulfonamide group), 164.6 (1C, C=O), 166.4 (1C, C–Cl), 169.2 (1C, C–NHSO2–), 169.9 (1C, C–NH–), 181.4 (1C, C–NHNCO– triazine ring); LC–MS (m/z): 498.07 (M\(^+\)), Anal. Caled. For C\(_9\)H\(_4\)Cl\(_2\)N\(_5\)O, C – 37.91, H – 2.12, N – 29.48; Found: C – 37.93, H – 2.10, N – 29.45%.

2.3. Preparation of 4-\(((4-chloro-6-(2-isonicotinoylhydrazinyl)-1,3,5-triazin-2-ylamino)-N-(pyrimidine-2-yl)benzenesulfonylamide \) (2)

A mixture of \(N'(4,6-dichloro-1,3,5-triazin-2-yl)isonicotinohydrazide \) (0.01 mol) in acetonitrile (15 mL) and 4-amino-N-(pyrimidine-2-yl)benzenesulfonylamide (0.01 mol) was taken in a conical flask. To this mixture, 4% NaOH was added drop-wise at room temperature and was stirred for 3 h. The reaction mixture was then poured onto crushed ice with constant stirring and neutralized with dil. HCl. The solid obtained was filtered, washed with water, dried and recrystallized from 1,4-dioxane. Yield: 70.0%; m.p.: 235 °C; IR (KBr, \(\upsilon, cm^{-1}\)): 788 (C–Cl, Stretching), 895 (S–N–O, stretching), 1135 (S–O, stretching in SO2), 1392 (N–H, bending), 1640 (C–C, stretching), 1690 (C–O, stretching), 1890 (C–N, stretching), 3035 (C–H, stretching in aromatic), 3445 (N–H, stretching in amine); \(^1\)H NMR (300 MHz, DMSO-d6, \(\delta, ppm\)): 6.54 (2H, Ar–NH–triazine), 6.72 (1H, triazine–NH–NH–), 6.93 (1H, pyrimidine), 7.1–7.83 (4H, Ar–H), 8.03 (1H, –SO2NH–), 8.87 (2H, pyrimidine), 9.78 (2H, pyridine), 3448 (N–H, stretching in amine); \(^13\)C NMR (100 MHz, DMSO-d6, \(\delta, ppm\)): 164.1 (1C, C–NH– attached with arylsulfonamide group), 164.6 (1C, C=O), 166.4 (1C, C–Cl), 169.2 (1C, C–NHSO2–), 169.9 (1C, C–NH–), 181.4 (1C, C–NHNCO– triazine ring); LC–MS (m/z): 498.07 (M\(^+\)), Anal. Caled. For C\(_9\)H\(_4\)Cl\(_2\)N\(_5\)O\(_3\)S, C – 45.74, H – 3.03, N – 28.07; Found: C – 45.75, H – 3.01, N – 28.04%.

2.4. Preparation of 4-\(((2-isonicotinoylhydrazinyl)-6-((aryl)amino)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonylamide \) (3a–v)

Intermediate compound 4-(4-chloro-6-(2-isonicotinoylhydrazinyl)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonylamide (2) (0.01 mol) in 1,4-dioxane (20 mL) was taken in a round bottom flask and different aromatic amines (0.01 mol) were added to it. To this mixture, 8% NaOH was added drop-wise and it was then refluxed for 2–4 h. Finally the reaction mixture was poured onto crushed ice with constant stirring and neutralized with dil. HCl. The product formed was filtered, washed with cold water, dried and recrystallized from methanol.

2.4.1. Physical constants and characterization of 4-\(((2-isonicotinoylhydrazinyl)-6-(phenyl amino)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonylamide \) (3a)

Yield: 63.0%; m.p.: 265–268 °C; IR (KBr, \(\upsilon, cm^{-1}\)): 795 (C–H, bending in aromatic), 985 (S–N, stretching), 1120 (S–O, stretching in SO2), 1392 (N–H, bending), 1640 (C–C, stretching), 1690 (C–O, stretching), 1890 (C–N, stretching), 3038 (C–H, stretching in aromatic), 3448 (N–H, stretching in amine); \(^1\)H NMR (300 MHz, DMSO-d6, \(\delta, ppm\)): 6.64 (2H, Ar–N–CO–), 6.72 (1H, triazine–NH–NH–), 7.82 (d, 2H, J = 7.9 Hz, C\(_2\)-H & C\(_3\)-H pyridine ring), 8.89 (d, 2H, J = 7.8 Hz, C\(_2\)-H & C\(_3\)-H pyridine ring), 9.74 (s, 1H, \(–NH–CO–\)); \(^13\)C NMR (100 MHz, DMSO-d6, \(\delta, ppm\)): 164.9 (1C, C=O), 169.2 (2C, C–C, Cl), 184.8 (1C, C–NH– triazine ring); LC–MS (m/z): 284.0 (M\(^+\)), Anal. Caled. For C\(_9\)H\(_4\)Cl\(_2\)N\(_5\)O\(_3\), C – 37.92, H – 2.12, N – 29.48; Found: C – 37.93, H – 2.10, N – 29.45%.
24.4. Physical constants and characterization of 4-(4-(4-bromophenylamino)-6-(2-isonicotinoylhydrazinyl)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonylamide (3b)

Yield: 72.0%, m.p. 259 °C; IR (KBr, ν cm⁻¹): 530 (C-Br, stretching), 780 (C-H, bending in aromatic), 898 (S-N, stretching), 1158 (S=O, stretching in SO₂), 1592 (N-H, bending), 1648 (C=C, stretching), 1730 (C=O, stretching), 1890 (C=N, stretching), 3025 (C-H, stretching in aromatic), 3059 (C-H, stretching in aromatic ring), 3447 (N-H, stretching in amine); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 6.67 (s, 2H, Ar-NH-triazine), 6.84 (s, 1H, triazine-NH–NH–), 6.92 (t, 1H, pyrimidine), 7.03–7.64 (m, 8H, Ar–H), 7.86 (d, 2H, J = 7.9 Hz, C₂H–C₂H–pyridine ring), 8.14 (s, 1H, –SO₂–NH–), 8.87 (d, 2H, pyrimidine), 8.95 (d, 2H, J = 7.6 Hz, C₂H & C₅H–pyridine ring), 9.82 (s, 1H, –NH–CO–); ¹³C NMR (100 MHz, DMSO-d₆, δ ppm): 164.3 (1C, C–N– attached with arylsulfonylamide group), 164.9 (1C, C=O), 168.7 (1C, C–NH–Ar), 169.4 (1C, C–NH–SO₂–), 176.8 (1C, C–NH–HCO– triazine ring); LC-MS (m/z): 555.15 (M⁺), Anal. Calcd. For C₅₂H₄₅N₁₃O₁₀S, C = 54.05, H = 3.81, N = 27.73; Found: C = 54.12, H = 3.90, N = 26.77%.

24.4.5. Physical constants and characterization of 4-(4-(4-chlorophenylamino)-6-(2-isonicotinoylhydrazinyl)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonylamide (3e)

Yield: 70.0%, m.p. 250 °C; IR (KBr, ν cm⁻¹): 680 (C–Cl, stretching), 781 (C-H, bending in aromatic), 890 (S-N, stretching), 1160 (S=O, stretching in SO₂), 1612 (N-H, bending), 1658 (C=C, stretching), 1890 (C=N, stretching), 3142 (C-H, stretching in aromatic), 3419 (N-H, stretching in amine); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 6.62 (s, 2H, Ar–NH–triazine), 6.83 (s, 1H, triazine–NH–NH–), 6.97 (t, 1H, pyrimidine), 7.13–7.65 (m, 8H, Ar–H), 7.87 (d, 2H, J = 7.8 Hz, C₂H & C₅H–pyridine ring), 8.15 (s, 1H, –SO₂–NH–), 8.83 (d, 2H, pyrimidine), 8.94 (d, 2H, J = 7.7 Hz, C₂H & C₅H–pyridine ring), 9.81 (s, 1H, –NH–CO–); ¹³C NMR (100 MHz, DMSO-d₆, δ ppm): 164.4 (1C, C–N– attached with arylsulfonylamide group), 164.8 (1C, C=O), 168.8 (1C, C–NH–Ar), 169.5 (1C, C–NH–SO₂–), 176.7 (1C, C–NH–HCO– triazine ring); LC-MS (m/z): 589.12 (M⁺), Anal. Calcd. For C₅₂H₄₁Cl₁₇N₁₃O₁₀S, C = 50.89, H = 3.42, N = 26.11; Found: C = 50.85, H = 3.44, N = 26.01%.

24.4.6. Physical constants and characterization of 4-(4-(2,5-dichlorophenylamino)-6-(2-isonicotinoylhydrazinyl)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonylamide (3f)

Yield: 69.0%, m.p. 240 °C; IR (KBr, ν cm⁻¹): 658 (C–Cl, stretching), 781 (C-H, bending in aromatic), 896 (S-N, stretching), 1151 (S=O, stretching in SO₂), 1615 (N-H, bending), 1657 (C=C, stretching), 1747 (C–O, stretching), 1889 (C=N, stretching), 3047 (C-H, stretching in aromatic), 3406 (C-H, stretching in aromatic ring); 3449 (N-H, stretching in amine); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 6.68 (s, 2H, Ar–NH–triazine), 6.85 (s, 1H, triazine–NH–NH–), 6.99 (t, 1H, pyrimidine), 7.09–7.64 (m, 6H, Ar–H), 7.76 (s, 1H, –NH–CO–); ¹³C NMR (100 MHz, DMSO-d₆, δ ppm): 164.2 (1C, C–N– attached with arylsulfonylamide group), 164.8 (1C, C=O), 168.8 (1C, C–NH–Ar), 169.6 (1C, C–NH–SO₂–), 176.9 (1C, C–NH–HCO– triazine ring); LC-MS (m/z): 589.12 (M⁺), Anal. Calcd. For C₅₂H₄₁Cl₁₇N₁₃O₁₀S, C = 50.89, H = 3.42, N = 26.11; Found: C = 50.77, H = 3.43, N = 26.11%.

24.4.7. Physical constants and characterization of 4-(4-(2,6-dichlorophenylamino)-6-(2-isonicotinoylhydrazinyl)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonylamide (3g)

Yield: 62.0%, m.p. 270 °C; IR (KBr, ν cm⁻¹): 645 (C–Cl, stretching), 789 (C-H, bending in aromatic), 894 (S-N, stretching...
ing), 1157 (S–O, stretching in SO₂), 1622 (N–H, bending), 1659 (C–C, stretching), 1750 (C–O, stretching), 1885 (C–N, stretching), 3050 (C–H, stretching in aromatic ring), 3453 (N–H, stretching in amine); 1H NMR (300 MHz, DMSO-d₆, δ, ppm): 6.67 (s, 2H, Ar–NH–triazine), 6.84 (s, 1H, triazine–NH–NH–), 6.94 (t, 1H, pyrimidine), 7.01–7.65 (m, 7H, Ar–H), 7.83 (d, 2H, J = 7.7 Hz, C₃H₂–H & C₂H₂–pyridine ring), 8.18 (s, 1H, SO₂–NH–), 8.84 (d, 2H, pyrimidine), 8.96 (d, 2H, J = 7.9 Hz, C₂H₂ & C₃H₂–pyridine ring), 9.87 (s, 1H, –NH–CO–); 13C NMR (100 MHz, DMSO-d₆, δ, ppm): 164.6 (1C, C–NH– attached with arylsulfonamide group), 164.7 (1C, C–O), 168.5 (1C, C–NH–Ar), 169.2 (1C, C–NHSO₂–), 176.5 (1C, C–NHNHC– triazine ring); LC–MS (m/z): 623.08 (M⁺), Anal. Calcd. For: C₂₀H₁₈N₁₄O₈S C – 48.08, H – 3.07, N – 24.67; Found: C – 48.09, H – 3.13, N – 24.68%.

2.4.8. Physical constants and characterization of 4-(4-(4-fluorophenylamino)-6-(2-isocytosinoylhydrazyl)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonamide (3k)

Yield: 75.0%, m.p. 240 °C; IR (KBr, ν, cm⁻¹): 791 (C–H, bending in aromatic), 908 (S–N, stretching), 1030 (C–F, stretching), 1152 (S–O, stretching in SO₂), 1622 (N–H, bending), 1652 (C–C, stretching), 1753 (C–O, stretching), 1875 (C–N, stretching), 3050 (C–H, stretching in aromatic), 3093 (C–H, stretching in aromatic ring), 3462 (N–H, stretching in amine); 1H NMR (300 MHz, DMSO-d₆, δ, ppm): 6.66 (s, 2H, Ar–NH–triazine), 6.84 (s, 1H, triazine–NH–NH–), 6.97 (t, 1H, pyrimidine), 7.12–7.83 (m, 8H, Ar–H), 7.89 (d, 2H, J = 7.9 Hz, C₃H₂–H & C₂H₂–pyridine ring), 8.16 (s, 1H, SO₂–NH–), 8.83 (d, 2H, pyrimidine), 8.98 (d, 2H, J = 7.7 Hz, C₂H₂ & C₃H₂–pyridine ring), 9.89 (s, 1H, –NH–CO–); 13C NMR (100 MHz, DMSO-d₆, δ, ppm): 164.2 (1C, C–NH– attached with arylsulfonamide group), 164.8 (1C, C–O), 168.6 (1C, C–NH–Ar), 169.5 (1C, C–NHSO₂–), 176.4 (1C, C–NHNHC–triazine ring); LC–MS (m/z): 573.15 (M⁺), Anal. Calcd. For: C₂₃H₂₀N₁₄O₈S C – 52.35, H – 3.51, N – 26.86; Found: C – 52.37, H – 3.50, N – 26.89%.

2.4.9. Physical constants and characterization of 4-(4-(4-isocytosinoylhydrazyl)-6-(o-tolylamino)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonamide (3l)

Yield: 78.0%, m.p. 260 °C; IR (KBr, ν, cm⁻¹): 710 (C–H, bending in aromatic), 902 (S–N, stretching), 1149 (S–O, stretching in SO₂), 1622 (N–H, bending), 1651 (C–C, stretching), 1749 (C–O, stretching), 1872 (C–N, stretching), 3462 (N–H, stretching in amine), 3630 (C–H, stretching in aromatic); 2890 (C–H, stretching in –CH₃), 3086 (C–H, stretching in aromatic ring); 1H NMR (DMSO-d₆, δ, ppm): 2.12 (s, 3H, –CH₃), 6.61 (s, 2H, Ar–NH–triazine), 6.80 (s, 1H, triazine–NH–NH–), 6.90 (t, 1H, pyrimidine), 6.98–7.77 (m, 8H, Ar–H), 7.86 (d, 2H, J = 7.7 Hz, C₃H₂–H & C₂H₂–pyridine ring), 8.10 (s, 1H, SO₂–NH–), 8.85 (d, 2H, pyrimidine), 8.94 (d, 2H, J = 7.9 Hz, C₂H₂ & C₃H₂–pyridine ring), 9.87 (s, 1H, –NH–CO–); 13C NMR (100 MHz, DMSO-d₆, δ, ppm): 17.8 (1C, –CH₃), 164.2 (1C, C–NH– attached with arylsulfonamide group), 164.6 (1C, C–O), 168.4 (1C, C–NH–Ar), 169.6 (1C, C–NHSO₂–), 176.5 (1C, C–NHNHC–triazine ring); LC–MS (m/z): 583.19 (M⁺), Anal. Calcd. For: C₂₃H₂₀N₁₄O₈S C – 55.56, H – 4.32, N – 26.40; Found: C – 55.55, H – 4.30, N – 26.42%.

2.4.10. Physical constants and characterization of 4-(4-(2-isocytosinoylhydrazyl)-6-(p-tolylamino)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonamide (3j)

Yield: 73.0%, m.p. 225 °C; IR (KBr, ν, cm⁻¹): 715 (C–H, bending in aromatic), 905 (S–N, stretching), 1153 (S–O, stretching in SO₂), 1628 (N–H, bending), 1649 (C–C, stretching), 1753 (C–O, stretching), 1868 (C–N, stretching), 2879 (C–H, stretching in –CH₃), 3048 (C–H, stretching in aromatic), 3091 (C–H, stretching in aromatic ring), 3458 (N–H, stretching in amine); 1H NMR (300 MHz, DMSO-d₆, δ, ppm): 2.07 (s, 3H, –CH₃), 6.60 (s, 2H, Ar–NH–triazine), 6.79 (s, 1H, triazine–NH–NH–), 6.89 (t, 1H, pyrimidine), 7.04–7.73 (m, 8H, Ar–H), 7.87 (d, 2H, J = 7.9 Hz, C₂H₂ & C₃H₂–pyridine ring), 8.08 (s, 1H, SO₂–NH–), 8.86 (d, 2H, pyrimidine), 8.94 (d, 2H, J = 7.9 Hz, C₂H₂ & C₃H₂–pyridine ring), 9.80 (s, 1H, –NH–CO–); 13C NMR (100 MHz, DMSO-d₆, δ, ppm): 21.6 (1C, –CH₃), 164.0 (1C, C–NH– attached with arylsulfonamide group), 164.8 (1C, C–O), 168.9 (1C, C–NH–Ar), 169.7 (1C, C–NHSO₂–), 176.4 (1C, C–NHNHC–triazine ring); LC–MS (m/z): 569.17 (M⁺), Anal. Calcd. For: C₂₃H₂₀N₁₄O₈S C – 54.82, H – 4.07, N – 27.05; Found: C – 54.84, H – 4.05, N – 27.09%.
Synthesis of benzenesulfonamide derivatives

J = 7.7 Hz, C2-H & C6-H pyridine ring), 9.80 (s, 1H, –NH–CO–); 13C NMR (100 MHz, DMSO-d6, δ ppm): 17.6 (2C, –CH3), 164.2 (1C, C-NH– attached with arylsulfonamide group), 164.8 (1C, C=O), 168.4 (1C, C–NH=Ar), 169.7 (1C, C–NHNHC– triazine ring); LC–MS (m/z): 583.19 (M+), Anal. Calcd. For: C26H24N10O6S, C – 55.56, H – 4.32, N – 26.40; Found: C – 55.55, H – 4.34, N – 26.41%.

2.4.13. Physical constants and characterization of 4-(4-[(2-isocinotioylhydrazinyl)-6-[(3-(trifluoromethyl)phenylamino)-1,3,5-triazin-2-ylamino]-N-(pyrimidin-2-yl)benzenesulfonamide (3m)

Yield: 68.0%, m.p. 300 °C; IR (KBr, ν cm−1): 727 (C–H, bending in aromatic), 918 (S-N, stretching), 1035 (C-F, stretching), 1147 (S=O, stretching in SO2), 1632 (N-H, bending), 1657(C–H, stretching), 1782 (C=O, stretching), 1864 (C=N, stretching), 2879 (C=H, stretching in –CH3), 3092 (C–H, stretching in aromatic ring), 3455 (N–H, stretching in amine), 1H NMR (300 MHz, DMSO-d6, δ ppm): 6.68 (2H, Ar–NH–triazine), 6.86 (s, 1H, triazine–NH–NH–), 6.98 (t, 1H, pyrimidine), 7.08–7.65 (m, 7H, Ar–H), 7.71 (s, 1H, Ar–H), 7.87 (d, 2H, J = 7.9 Hz, C2-H & C4’-H pyridine ring), 8.16 (s, 1H, –SO2–NH–), 8.88 (d, 2H, pyrimidine), 8.98 (d, 2H, J = 7.5 Hz, C2-H & C4’-H pyridine ring), 9.89 (s, 1H, –NH–CO–); 13C NMR (100 MHz, DMSO-d6, δ ppm): 124.4 (1C, –CF3), 164.1 (1C, C–NH– attached with arylsulfonamide group), 164.8 (1C, C=O), 168.4 (1C, C–NH=Ar), 169.6 (1C, C–NHNHC– triazine ring); LC–MS (m/z): 623.14 (M+), Anal. Calcd. For: C26H24F3N10O6S, C – 53.33, H – 3.96, N – 25.08; Found: C – 53.06, H – 3.25, N – 24.75%.

2.4.14. Physical constants and characterization of 4-(4-[(2-isocinotioylhydrazinyl)-6-[(3-(trifluoromethyl)phenylamino)-1,3,5-triazin-2-ylamino]-N-(pyrimidin-2-yl)benzenesulfonamide (3n)

Yield: 63.0%, m.p. 275 °C; IR (KBr, ν cm−1): 730 (C–H, bending in aromatic), 917 (S-N, stretching), 1015 (C-F, stretching), 1152 (S=O, stretching in SO3), 1628 (N-H, bending), 1639 (N-H, bending), 1649 (C=C, stretching), 1785 (C=O, stretching), 1862 (C=N, stretching), 2875 (C=H, stretching in –CH3), 3098 (C–H, stretching in amine), 3451 (N–H, stretching in amine); 1H NMR (300 MHz, DMSO-d6, δ ppm): 6.64 (2s, 2H, Ar–NH–triazine), 6.84 (s, 1H, triazine–NH–NH–), 6.95 (t, 1H, pyrimidine), 7.11–7.67 (m, 8H, Ar–H), 7.88 (d, 2H, J = 7.9 Hz, C2-H & C4’-H pyridine ring), 8.15 (s, 1H, –SO2–NH–), 8.89 (d, 2H, pyrimidine), 8.97 (d, 2H, J = 7.8 Hz, C2-H & C4’-H pyridine ring), 9.87 (s, 1H, –NH–CO–); 13C NMR (100 MHz, DMSO-d6, δ ppm): 124.5 (1C, –CF3), 164.0 (1C, C–NH– attached with arylsulfonamide group), 164.7 (1C, C=O), 168.5 (1C, C–NH=Ar), 169.4 (1C, C–NHNHC– triazine ring); LC–MS (m/z): 623.14 (M+), Anal. Calcd. For: C26H24F3N10O6S, C – 53.38, H – 3.96, N – 25.08; Found: C – 53.06, H – 3.25, N – 24.72%.

2.4.15. Physical constants and characterization of 4-(4-[(2-isocinotioylhydrazinyl)-6-[(4-methoxyphenylamino)-1,3,5-triazin-2-ylamino]-N-(pyrimidin-2-yl)benzenesulfonamide (3o)

Yield: 67.0%, m.p. 289 °C; IR (KBr, ν cm−1): 728 (C–H, bending in aromatic), 919 (S-N, stretching), 1151 (S=O, stretching in SO2), 1624 (N-H, bending), 1644 (C=C, stretching), 1779 (C=O, stretching), 1859 (C=N, stretching), 2835 (C=O–CH3, stretching), 2871 (C–H, stretching in –CH3), 3092 (C–H, stretching in aromatic ring), 3438 (N–H, stretching in amine); 1H NMR (300 MHz, DMSO-d6, δ ppm): 3.83 (s, 3H, –OCH3), 6.59 (s, 2H, Ar–NH–triazine), 6.79 (s, 1H, triazine–NH–NH–), 6.89 (t, 1H, pyrimidine), 7.01–7.62 (m, 6H, Ar–H), 7.72 (s, 1H, Ar–H), 7.81 (d, 2H, J = 7.7 Hz, C2-H & C4’-H pyridine ring), 8.07 (s, 1H, –SO2–NH–), 8.82 (d, 2H, pyrimidine), 8.92 (d, 2H, J = 7.9 Hz, C2-H & C4’-H pyridine ring), 9.78 (s, 1H, –NH–CO–); 13C NMR (100 MHz, DMSO-d6, δ ppm): 52.8 (1C, –OCH3), 55.7 (1C, –OCH3), 164.0 (1C, C–NH– attached with arylsulfonamide group), 164.6 (1C, C=O), 168.5 (1C, C–NH=Ar), 169.3 (1C, C–NHNHC– triazine ring); LC–MS (m/z): 615.18 (M+), Anal. Calcd. For: C26H24F3N10O7S, C – 52.68, H – 4.09, N – 25.03; Found: C – 52.67, H – 4.08, N – 25.05%.

2.4.17. Physical constants and characterization of 4-(4-[(2-ethoxyphenylamino)-6-[(2-isocinotioylhydrazinyl)-1,3,5-triazin-2-ylamino]-N-(pyrimidin-2-yl)benzenesulfonamide (3q)

Yield: 59.0%, m.p. 304 °C; IR (KBr, ν cm−1): 723 (C–H, bending in aromatic), 925 (S-N, stretching), 1156 (S=O, stretching in SO2), 1175 (C–O, stretching in C–O–C), 1628 (N-H, bending), 1638 (N-H, bending), 1642 (C=C, stretching), 1781 (C=O, stretching), 1852 (C=N, stretching), 2873 (C–H, stretching in –CH3), 3084 (C–H, stretching in aromatic ring), 3431 (N–H, stretching in amine); 1H NMR (300 MHz, DMSO-d6, δ ppm): 1.31 (t, 3H, –OCH2CH3), 4.08 (q, 2H, –OCH2CH2), 6.60 (s, 2H, Ar–NH–triazine), 6.79 (s, 1H, triazine–NH–NH–), 6.92 (t, 1H, pyrimidine), 7.08–7.68 (m, 8H, Ar–H), 7.81 (d, 2H, J = 7.6 Hz, C2-H & C4’-H pyridine ring), 8.08 (s, 1H, –SO2–NH–), 8.83 (d, 2H, pyrimidine), 8.90 (d, 2H, J = 7.7 Hz, C2-H & C4’-H pyridine ring), 9.79 (s, 1H, –NH–CO–); 13C NMR (100 MHz, DMSO-d6, δ ppm): 14.6 (1C, C–OCH2CH3), 64.9 (1C, C–OCH2CH3), 164.2 (1C, C–NH–
attached with arylsulfonamide group), 164.8 (1C, C—O), 168.3 (1C, C—NH—Ar), 169.6 (1C, C-NHSO2—), 176.4 (1C, C-NHNHC— triazine ring). LC-MS (m/z): 599.18 (M+), Anal. Calcd. For: C2H2N1O2S, C = 50.04, H = 4.20, N = 25.70; Found: C = 54.07, H = 4.21, N = 24.57.

2.4.18. Physical constants and characterization of 4-[(4-[(2-isonicotinoylhydrazinyl)-6-(2-nitrophenylamino)-1,3,5-triazin-2-ylamino-N-((pyrimidin-2-yl)benzenesulfonamide (3r)
Yield: 70.0%, m.p. 269 °C; IR (KBr, ν cm⁻¹): 728 (C—H, bending in aromatic), 929 (S—N, stretching), 1154 (S=O, stretching in SO2), 1582 (S—O2, stretching), 1632, (N—H, bending), 1641 (C—C, stretching), 1778 (C—O, stretching), 1851 (C═N, stretching), 2878 (C—H, stretching in —CH2), 3081 (C—H, stretching in aromatic ring), 3441 (N—H, stretching in amine); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 6.67 (s, 2H, Ar—NH—triazine), 6.86 (s, 1H, triazine—NH—NH—), 6.95 (t, 1H, pyrimidine), 7.07–7.69 (m, 8H, Ar—H), 7.89 (d, 2H, J = 7.8 Hz, C2—H & C5—H pyridine ring), 8.17 (s, 1H, —SO2—NH—), 8.88 (d, 2H, pyrimidine), 8.99 (d, 2H, J = 8.0 Hz, C2—H & C5—H pyridine ring), 9.91 (s, 1H, —NH—CO—); ¹³C NMR (100 MHz, DMSO-d₆, δ ppm): 164.2 (1C, C—NH— attached with arylsulfonamide group), 164.8 (1C, C—NH—), 169.5 (1C, C—NHSO₂—), 176.6 (1C, C—NHNHC— triazine ring); LC-MS (m/z): 599.14 (M+), Anal. Calcd. For: C2H2N1O2S, C = 50.03, H = 3.35, N = 27.99.

2.4.19. Physical constants and characterization of 4-[(4-[(2-isonicotinoylhydrazinyl)-6-(3-nitrophenylamino)-1,3,5-triazin-2-ylamino)-N-((pyrimidin-2-yl)benzenesulfonamide (3s)
Yield: 65.0%, m.p. 298 °C; IR (KBr, ν cm⁻¹): 732 (C—H, bending in aromatic), 923 (S—N, stretching), 1142 (S=O, stretching in SO2), 1573 (C—O2, stretching), 1635 (N—H, bending), 1644 (C—C, stretching), 1775 (C═N, stretching), 1853 (C═N, stretching), 2883 (C—H, stretching in —CH2), 3088 (C—H, stretching in aromatic ring), 3442 (N—H, stretching in amine); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 6.66 (s, 2H, Ar—NH—triazine), 6.86 (s, 1H, triazine—NH—NH—), 6.97 (t, 1H, pyrimidine), 7.13–7.75 (m, 7H, Ar—H), 7.81 (s, 1H, Ar—H), 7.88 (d, 2H, J = 7.9 Hz, C2—H & C5—H pyridine ring), 8.16 (s, 1H, —SO2—NH—), 8.87 (d, 2H, pyrimidine), 8.98 (d, 2H, J = 7.8 Hz, C2—H & C5—H pyridine ring), 9.89 (s, 2H, —NH—CO—); ¹³C NMR (100 MHz, DMSO-d₆, δ ppm): 164.0 (1C, C—NH— attached with arylsulfonamide group), 164.7 (1C, C—O), 168.6 (1C, C—NH—Ar), 169.2 (1C, C-NHSO₂—), 176.3 (1C, C—NHNHC— triazine ring); LC-MS (m/z): 599.14 (M+). Anal. Calcd. For: C2H2N1O2S, C = 52.06, H = 3.53, N = 25.70; Found: C = 52.14, H = 3.61, N = 25.78.

2.4.20. Physical constants and characterization of 4-[(4-[(2-isonicotinoylhydrazinyl)-6-(4-nitrophenylamino)-1,3,5-triazin-2-ylamino)-N-((pyrimidin-2-yl)benzenesulfonamide (3t)
Yield: 66.0%, m.p. 288 °C; IR (KBr, ν cm⁻¹): 742 (C—H, bending in aromatic), 928 (S—N, stretching), 1146 (S=O, stretching in SO2), 1248 (C—O, stretching, ester), 1633 (N—H, bending), 1643 (C═C, stretching), 1742 (C═O, stretching in ester), 1856 (C═N, stretching), 2885 (C—H, stretching in —CH2), 3092 (C—H, stretching in aromatic ring), 3442 (N—H, stretching in amine); ¹H NMR (300 MHz, DMSO-d₆, δ ppm): 1.30 (t, 3H, —COOCH2CH₃), 4.33 (q, 2H, —CO—OCH3), 6.65 (s, 2H, Ar—NH—triazine), 6.86 (s, 1H, triazine—NH—NH—), 6.95 (t, 1H, pyrimidine), 7.07–7.81 (m, 8H, Ar—H), 7.86 (d, 2H, J = 7.8 Hz, C2—H & C5—H pyridine ring), 8.12 (s, 1H, —SO2—NH—), 8.87 (d, 2H, pyrimidine), 8.98 (d, 2H, J = 7.9 Hz, C2—H & C5—H pyridine ring), 9.91 (s, 1H, —NH—CO—); ¹³C NMR (100 MHz, DMSO-d₆, δ ppm): 14.4 (1C, — COOCH2CH₃), 60.7 (1C, — COOCH2CH₃), 164.3 (1C, C—NH— attached with arylsulfonamide group), 164.8 (1C, C—O), 165.7 (1C, —COOCH2CH₃), 166.8 (1C, C—NH—Ar), 169.2 (1C, C-NHSO₂—), 176.3 (1C, C—NHNHC— triazine ring); LC-MS (m/z): 627.18 (M+). Anal. Calcd. For: C2H2N1O2S, C = 53.58, H = 4.01, N = 24.55; Found: C = 53.57, H = 4.05, N = 24.54.
2.5. Antibacterial assay

The synthesized compounds were screened for their antibacterial activity against Gram Positive bacteria [*Staphylococcus aureus* (MTCC-96), *Staphylococcus pyogenes* (MTCC-442)] and Gram-negative bacteria [*Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688)]. The antibacterial activity was carried out by preparing serial dilution of given solution using the Mueller Hinton Broth dilution method (Becton Dickinson, USA) [9,6,7]. The standard strains used for antimicrobial activity were procured from the Institute of Microbial Technology, Chandigarh. The compounds (3a–v) were screened for their antibacterial activity in triplicate sets against these bacteria at different concentrations of 1000, 500, 250, and 100 μg/mL. The drugs which were found to be active in primary screening were further diluted to obtain 100, 50, and 25 μg/mL concentrations. Ten μg/mL suspensions were further inoculated on appropriate media and growth was noted after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition was taken as minimum inhibitory concentration (MIC). The test mixture should contain 10^9 cells/mL. The standard drug used in this study was ampicillin for evaluating antibacterial activity which showed (100, 100, 250, and 100 μg/mL) MIC against *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. pyogenes*, respectively.

2.6. Antifungal assay

Similarly, various concentrations of compounds (3a–v) were tested for antifungal activity in triplicate sets against *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* at various concentrations of 1000, 500, 250, 200, and 100 μg/mL and the obtained results were recorded in the form of primary and secondary screening. The synthesized compounds were prepared as stock solution diluted to 1000 μg/mL concentration. The compounds which were found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition was taken as MIC. The test mixture should contain 10^8 spores/mL MIC. Griseofulvin was used as a standard drug for antifungal activity, which showed (500, 100, and 100 μg/mL) MIC against *C. albicans* and *A. niger*, respectively.

![Scheme 1: Synthetic route for final compounds (3a–v).](image-url)
with the triazine ring and –NHCO appeared at 3412 cm$^{-1}$. Medium intensity absorption band was exhibited at 3038 cm$^{-1}$ due to C–H stretching in the pyridine ring and it closely resembled monosubstituted benzene derivatives, while C–H stretching in the aromatic ring appeared at 3020 cm$^{-1}$. The stretching bands appearing over the range 1640 and 1890 cm$^{-1}$ showed the presence of C–C and C=N stretching in pyridine, pyrimidine and phenyl rings respectively. Strong intensity absorption peak at 795 cm$^{-1}$ showed C–H bending vibration in the aromatic ring. Medium intensity band appeared at 895 cm$^{-1}$ due to the presence of S–N stretching in compound (3a). Strong 1R band appearing at 1690 cm$^{-1}$ showed C=O stretching and the medium intensity absorption peak observed at 1120 cm$^{-1}$ exhibited the presence of S=O stretching in SO$_2$.

In $^1$H NMR spectra of the titled compound (3a), five singlets were observed for five protons of –NH i.e., a –NH proton attached with triazine and –NHCO appeared at $\delta = 6.82$ ppm, two –NH protons attached with the triazine and aryl group exhibited signal at $\delta = 6.64$ ppm, a –NH proton in sulfonamide linkage showed chemical shift at $\delta = 8.13$ ppm and –NH attached with the carbonyl group displayed chemical shift at $\delta = 9.78$ ppm. Due to the presence of nine aromatic protons (Ar–H) a multiplet was observed at $\delta = 6.93$–7.85 ppm. A chemical shift was observed at $\delta = 6.98$–8.89 ppm due to the presence of seven multiplet (Ar–H) in the pyridine and pyrimidine rings of the titled compound. The final compound (3a) possessed three moieties pyridine, pyrimidine and 1,3,5-triazine. On the basis of $^{13}$C NMR of the final compound (3a), the chemical shift varied from $\delta = 113.0$ to 176.5 ppm. Carbon nucleus under the influence of strong electronegative environment appeared downfield i.e., carbonyl carbon present in amide linkage directly attached to nitrogen exhibited chemical shift value at $\delta = 164.4$ ppm. Carbon present in the pyrimidine nucleus directly linked to nitrogen atoms appeared downfield at $\delta = 169.3$ ppm. Three carbons of triazine nucleus displayed chemical shift value at $\delta = 161.4$, 168.9 and 176.7 ppm corresponding to carbons attached with the phenyl sulfonamide group, aniline and –NH of the hydrazide group, respectively.

### 3.2. Antimicrobial activity

Many of the newly synthesized compounds were found to exhibit good to excellent antimicrobial activity. The individual minimum inhibitory concentration (MIC, µg/mL) values of tested compounds (3a–v) against the test microbes are listed in Table 1 along with MIC values of reference compounds ampicillin (for bacteria) and griseofulvin (for fungi). The results revealed that majority of synthesized compounds showed varying degrees of inhibition against the tested panel of species. The obtained antimicrobial activity of tested compounds could be correlated to structural variations and modifications of the respective compounds. From antimicrobial activity data (Table 1), it is observed that compounds 3a (–H), 3b (–4-Br), 3c (–2-Cl), 3f (–2,5-(Cl)2), 3i (–2-CH$_3$), 3j (–2,4-(CH$_3$)$_2$), 3n (–2,4-(CF$_3$)$_2$), 3p (–2,4-(OCH$_3$)$_2$), 3r (–2-NO$_2$) and 3s (–3-NO$_2$) possessed good activity against E. coli at MIC 100 µg/mL. Compounds 3g (–2,6-(Cl)$_2$), 3h (–4-F), 3i (–4-NO$_2$) and 3v (–4-COOCH$_3$)$_2$ showed excellent activity against E. coli at MIC 50 µg/mL, respectively. Compounds 3a (–H), 3d (–3-Cl), 3e (–4-F), 3f (–2,6-(CH$_3$)$_2$), 3r (–2-NO$_2$), 3s (–3-NO$_2$) and 3t (–4-NO$_2$) exhibited very good activity against

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<th>Sr. No.</th>
<th>–R</th>
<th>Minimum inhibitory concentration (MIC) in µg/mL</th>
<th>Minimum inhibitory concentration (MIC) in µg/mL</th>
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**P. aeruginosa** at MIC 100 µg/mL. Compounds 3b (–4-Br), 3c (–2-CI), 3e (–4-F), 3f (–2,6-(CH3)2), 3n (–4-CF3) and 3u (–4-COOH) possessed very good activity against *S. aureus* at MIC 100 µg/mL, while compounds 3t (–4-NO2) and 3v (–4-COOC2H5) flaunted excellent activity against *S. aureus* at MIC 50 µg/mL. Among all the synthesized compounds, 3f (–2,5-(Cl)2), 3m (–3-Cl) and 3n (–4-CF3) possessed very good activity against *S. pyogenes* at MIC 100 µg/mL. All the synthesized compounds, 3v (–2,4,6-(Cl)3), 3u (–4-NO2) and 3v (–4-COOH) exhibited very good activity against *S. aureus* at MIC 50 µg/mL.

### 4. Structure–activity relationship (SAR)

The substitution pattern of s-triazine derivatives was carefully selected to confer different electronic environment to molecules. The results from antimicrobial activity suggested that s-triazine derivatives were remarkably influenced by various substituents on the benzene ring. Majority of the synthesized compounds of this series exhibited significant antibacterial and moderate antifungal activity. Compounds 3g, 3h, 3i and 3j exhibited highest inhibition against bacterial strains *S. aureus* and *E. coli* at MIC 50 µg/mL. Furthermore, compounds 3g and 3h showed significant inhibition against fungi strains *C. albicans* at MIC 50 µg/mL. The data revealed that incorporation of electron withdrawing groups like halogen, nitro and ester on the phenyl ring enhanced antimicrobial activity against selected microorganisms. Thus, our aim was to explore SAR trends and to find out lead molecule for further optimization.

### 5. Conclusions

A series of twenty-two s-triazine derivatives were synthesized and tested for their in vitro antibacterial activity against four strains of bacteria (Gram-positive, Gram-negative). The preliminary in vitro antibacterial and antifungal screening results of new 1,3,5-triazine-isonicotinohydrazide derivatives exhibited remarkable antimicrobial potency. The newly synthesized compounds differed in their corresponding antimicrobial activity depending on the type of substituents on the phenyl ring. Presence of the electron withdrawing group on the aromatic ring increased the antimicrobial activity compared to compounds with electron donating groups. Based on the results, we can further optimize the above compounds by substituting a series of electron withdrawing groups on the aromatic ring and selectively modifying them. Thus, it may be considered a promising lead for further design and development of new chemical entities. The results described here, demand further investigations in our laboratory using a forward chemical genetic approach for finding lead molecules as antimicrobial agents.

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### References


