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ORIGINAL ARTICLE

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

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KEYWORDS

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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.

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],

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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 F_{245} (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 using DMSO-d_6 as solvent and TMS as an internal standard. Mass spectra were obtained on SHIMADZU LC–MS 2010 spectrophotometer. In the conventional method, compounds were synthesized using Random synthesizer.

2.2. Preparation of *N′-(4,6-dichloro-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 formed was filtered, washed with water, dried and recrystallized from acetone. Yield: 80.0%; m.p.: 180 °C; IR (KBr, ν, cm^{-1}): 780 (C–Cl, Stretching), 1587 (N–H, bending), 1640 (C═C, stretching), 1690 (C═O, stretching), 1890 (C═N, stretching), 3444 (N–H, stretching in amine); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.72 (s, 1H, triazine-N*H*–NH–), 7.82 (d, 2H, J = 7.9 Hz, C_3-H & C_5-H pyridine ring), 8.89 (d, 2H, J = 7.8 Hz, C_2-H & C_6-H pyridine ring), 9.74 (s, 1H, –N*H*–CO–); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 164.9 (1C, C═O), 169.2 (2C, C–Cl), 184.8 (1C, C–NH– triazine ring); LC–MS (m/z): 284.0 (M^+), Anal. Calcd. For $C_9H_6Cl_2N_6O$, C – 37.92, 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-triazine-2-ylamino)-N-(pyrimidine-2-yl)benzenesulfonamide (**2**)

A mixture of *N′*-(4,6-dichloro-1,3,5-triazine-2-yl) isonicotinohydrazide (0.01 mol) in acetone (15 mL) and 4-amino-*N*-(pyrimidine-2-yl)benzenesulfonamide (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, ν, cm^{-1}): 788 (C–Cl, Stretching), 895 (S–N, stretching), 1135 (S═O, stretching in SO_2), 1592 (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-d_6, δ, ppm): 6.54 (s, 2H, Ar–N*H*–triazine), 6.72 (s, 1H, triazine–N*H*–NH–), 6.93 (t, 1H, pyrimidine), 7.1–7.83 (d, 4H, Ar–H), 7.86 (d, 2H, J = 8.0 Hz, C_3-H & C_5-H pyridine ring), 8.03 (s, 1H, –SO_2–N*H*–), 8.87 (d, 2H, pyrimidine), 8.95 (d, 2H, J = 7.7 Hz, C_2-H & C_6-H pyridine ring), 9.78 (s, 1H, –N*H*–CO–); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 164.1 (1C, C–NH– attached with arylsulfonamide group), 164.6 (1C, C═O), 166.4 (1C, C–Cl), 169.2 (1C, C–NHSO$_2$–), 169.9 (1C, C–NH–), 181.4 (1C, C–NHNHCO– triazine ring); LC–MS (m/z): 498.07 (M^+), Anal. Calcd. For $C_{19}H_{15}ClN_{10}O_3S$, C – 45.74, H – 3.03, N – 28.07; Found: C – 45.75, H – 3.01, N – 28.04%.

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

Intermediate compound 4-(4-chloro-6-(2-isonicotinoylhydrazinyl)-1,3,5-triazin-2-ylamino)-*N*-(pyrimidin-2-yl)benzenesulfonamide (**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-(4-(2-isonicotinoylhydrazinyl)-6-(phenyl amino)-1,3,5-triazin-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonamide (**3a**)

Yield: 63.0%; m.p.: 265–268 °C; IR (KBr, ν, cm^{-1}): 795 (C–H, bending in aromatic), 895 (S–N, stretching), 1120 (S═O, stretching in SO_2), 1592 (N–H, bending), 1640 (C═C, stretching), 1690 (C═O, stretching), 1890 (C═N, stretching), 3020 (C–H, stretching in aromatic ring), 3038 (C–H, stretching in aromatic), 3448 (N–H, stretching in amine); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.64 (s, 2H, Ar–N*H*–triazine), 6.82 (s, 1H, triazine–N*H*–NH–), 6.91 (t, 1H, pyrimidine), 7.02–7.62 (m, 9H, Ar–H), 7.84 (d, 2H, J = 7.8 Hz, C_3-H & C_5-H pyridine ring), 8.13 (s, 1H, –SO_2–N*H*–), 8.84 (d, 2H, pyrimidine), 8.98 (d, 2H, J = 7.9 Hz, C_2-H & C_6-H pyridine ring), 9.78 (s, 1H, –N*H*–CO–); ^{13}C NMR (100 MHz, DMSO-d_6, δ,