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Synthesis and study of 1,3,5-triazine based thiazole derivatives as antimicrobial agents

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Abstract A series of novel compounds *N*′-(4-(arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazides **(3a–l)** were synthesized by a series of multistep reactions. Newly synthesized compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Antimicrobial screening of title compounds **(3a–l)** was examined against Gram-positive bacteria (*Staphylococcus aureus*, *Streptococcus pyogenes*), Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) and three fungi (*Candida albicans*, *Aspergillus niger*, *Aspergillus clavatus*) by using serial broth dilution method. Synthesized compounds showed potent inhibitory action against test organisms. Screened compounds **3k** and **3l** were associated with considerably higher antibacterial and antifungal activities than commercially used antibiotics.

1. Introduction

Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents (Krchnak and Holladay, 2002). 1,3,5-Triazine analogs constitute an important class of the realm of heterocycles, which has attracted much synthetic interest due to their wide range of biological activities such as antimicrobial (Zhou et al., 2008) (Srinivas et al., 2006) (Baliani et al., 2006), anticancer, (Menicagli et al., 2004) (Garaj et al., 2005), antimalarial (Melato et al., 2008), and antiviral activity (Xiong et al., 2008). Profound medicinal applications associated with isonicotinohydrazide render them as useful structural units in drug research (Maccari et al., 2004). Thiazoles and their derivatives have found applications in drug development for the treatment of allergies (Hargrave et al., 1983), inflammation (Holla et al., 2003), bacterial infections (Desai et al., 2012a), HIV infections (Bell et al., 1995) and as new inhibitors of bacterial DNA gyrase B (Rudolph et al., 2001). Thiazole nucleus is also an integral part of all the available penicillins which have revolutionized the therapy of bacterial diseases (Oncu et al., 2004). Therefore, it was thought of interest to develop a system which combines bio-labile nuclei; 1,3,5-Triazine, isonicotinohydrazide and thiazole together in a molecular framework to see their additive effect on antimicrobial power.

The toxicity, side effects, and resistance of common pathogens to standard drugs play important roles in treatment fail-

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ure (Sonntag et al., 2004) (Puertoa et al., 2006). Therefore, searching for new antimicrobial agents with specific activity, possibly acting through mechanism, which are distinct from those of well-known classes is of prime interest. The above facts coupled with our desire to develop efficacious antimicrobial agents and in continuation of our work on heterocycles with biological interest (Desai et al., 2012b,c,d,e,f) prompted us to device an efficient and convenient synthetic method of hitherto unknown and new title compounds *N*′-(4-(arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazides **(3a–l)**. The antibacterial and antifungal results of these newly synthesized compounds are reported in this paper.

2. Experimental

2.1. Materials and physical measurements

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. Melting points were determined on an electro thermal melting point apparatus and are reported uncorrected. TLC on silica gel plates (Merck, 60, F_{254}) were used for purity checking and reaction monitoring. Column chromatography on silica gel (Merck, 70–230 mesh and 230–400 mesh ASTH for flash chromatography) was applied when necessary to isolate and purify the reaction products. Elemental analysis (% C, H, N) was carried out by a Perkin–Elmer 2400 CHN analyzer. IR spectra of all compounds were recorded on a Perkin–Elmer FT-IR spectrophotometer in KBr. ^{1}H NMR spectra were recorded on Varian Gemini 300 MHz and ^{13}C NMR spectra on Varian Mercury-400, 100 MHz in DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were scanned on a Shimadzu LC-MS 2010 spectrometer. Anhydrous reactions were carried out in oven-dried glassware in nitrogen atmosphere.

2.2. Preparation of N′-(4,6-dichloro-1,3,5-triazin-2-yl)isonicotinohydrazide 1

In a conical flask, 2,4,6-trichloro-1,3,5-triazine (0.01 mol) was taken in 20 mL acetone and isoniazid (i.e. isonicotinohydrazide) (0.01 mol) was added to it. 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 dilute HCl. The solid was filtered and washed with water and dried. The product was recrystallized from acetone. The product was purified by column chromatography using hexane–ethyl acetate (4:1) as eluent to get the compound **(1)**. Yield: 75%; m.p.: 180–182 °C; IR (KBr) υ_{max}/cm^{-1}: 3340, 3270, 3041, 1716, 1605, 1581, 1517, 767; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.57 (s, 1H, –NH-triazine), 7.72–8.87 (m, 4H, Ar–H), 9.08 (s, 1H, –CONH–); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 121.4, 137.3, 149.3, 164.3, 169.2, 171.8; LC-MS *(m/z)*: 284 (M^+); Anal. Calcd. for $C_9H_6Cl_2N_6O$: C-37.92, H-2.12, N-29.48; Found: C-37.88, H-2.17, N-29.44%.

2.3. Preparation of N′-(4-chloro-6-(thiazol-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide 2

In a conical flask, *N*′-(4, 6-dichloro-1,3,5-triazin-2-yl)isonicotinohydrazide **1** (0.01 mol) was taken in 20 mL acetone and thiazol-2-amine (0.01 mol) was added to it. To this mixture, 4% NaOH was added drop wise at room temperature (30 °C) and the mixture was stirred for 3 h. The solution was poured onto crushed ice with constant stirring and neutralized with dilute HCl. The solid was filtered, washed with water and dried. The product was recrystallized from ethanol. The product was purified by column chromatography using hexane–ethyl acetate (4:1) as eluent to get compound **2**. Yield: 71%; m.p.: 235–237 °C; IR (KBr) υ_{max}/cm^{-1}: 3356, 3320, 3270, 3041, 3010, 1711, 1602, 1582, 1513, 758; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.12 (s, 1H, NH-thiazole ring), 6.61 (s, 1H, –NH-triazine), 6.78–8.82 (m, 6H, Ar-H), 9.11 (s, 1H, –CONH–); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 111.5, 121.3, 136.8, 137.3, 149.4, 158.5, 164.2, 165.3, 168.1, 171.2; LC-MS *(m/z)*: 348 (M^+); Anal. Calcd. for $C_{12}H_9ClN_8OS$: C-41.32, H-2.60, N-32.13; Found: C-41.37, H-2.53, N-32.17%.

2.4. Preparation of N′-(4-(arylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazides 3a-l

In a round bottom flask, *N*′-(4-chloro-6-(thiazol-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide **2** (0.01 mol) and 1,4-dioxane (20 mL) was taken. To this mixture, different aromatic amines (0.01 mol) were added. The pH was adjusted to neutral by adding 8% NaOH and the reaction mixture was refluxed for 2 h. The reaction mixture was poured onto crushed ice with constant stirring and was neutralized with dilute HCl. The product was filtered, washed with cold water and dried. The product was recrystallized from methanol. The product was purified by column chromatography using hexane–ethyl acetate (4:1) as eluent to afford the title compounds.

2.4.1. N′-(4-(phenylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide 3a

Yield: 62%; brown crystalline solid; m.p.: 202–204 °C; IR (KBr) υ_{max}/cm^{-1}: 3380, 3350, 3282, 3022, 3010, 1710, 1605, 1589, 1516; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.64 (s, 1H, –NH-Ar group), 6.16 (s, 1H, NH-thiazole ring), 6.68 (s, 1H, -NH-triazine), 6.78–8.89 (m, 11H, Ar–H), 9.20 (s, 1H, –CONH–); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 111.7, 117.8, 121.7, 122.4, 129.5, 136.6, 137.7, 138.9, 149.7, 160.1, 163.7, 165.5, 167.9, 171.3; LC-MS *(m/z)*: 405 (M^+); Anal. Calcd. for $C_{18}H_{15}N_9OS$: C-53.32, H-3.73, N-31.09; Found: C-53.37, H-3.78, N-31.14%.

2.4.2. N′-(4-(4-bromophenylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide 3b

Yield: 60%; light brown solid; m.p.: 195–197 °C; IR (KBr) υ_{max}/cm^{-1}: 3374, 3352, 3276, 3025, 3017, 1714, 1610, 1582, 1514, 610; ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 5.69 (s, 1H, -NH-Ar group), 6.13 (s, 1H, NH-thiazole ring), 6.63 (s, 1H, –NH-triazine), 6.71–8.85 (m, 10H, Ar–H), 9.27 (s, 1H, –CONH–); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 111.5, 116.6, 118.7, 121.6, 132.6, 136.7, 137.4, 137.7, 149.6, 160.4, 163.7, 165.5, 167.4, 171.6; LC-MS *(m/z)*: 483 (M^+). Anal. Calcd. for $C_{18}H_{14}BrN_9OS$: C-44.64, H-2.91 N-26.03; Found C-44.70, H-2.98, N-26.10%.

2.4.3. N′-(4-(2-chlorophenylamino)-6-(thiazol-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide 3c

Yield: 65%; light yellow solid; m.p.: 198–200 °C; IR (KBr) υ_{max}/cm^{-1}: 3376, 3356, 3276, 3027, 3015, 1716, 1609, 1586,