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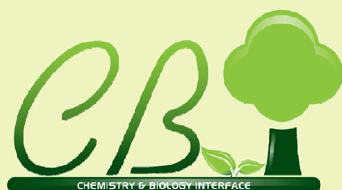

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Research Paper

Hypervalent iodine mediated synthesis of some new *N*-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-arylthiazol-2-yl)hydrazines and their evaluation as antibacterial and cytotoxic agents

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Abstract: A series of *N*-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-arylthiazol-2-yl)hydrazines **4a-h** have been synthesized by the treatment of *N*-(4,6-dimethylpyrimidin-2-yl)thiosemicarbazide **2** with *α*-tosyloxy ketones **3a-h** which, in turn, have been generated *in situ* by the reaction of enolizable methyl ketones with hypervalent iodine reagent, [hydroxy(tosyloxy)iodo]benzene, HTIB. These compounds were evaluated for their antibacterial activities against two Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). All the tested compounds exhibited variable activity against Gram-positive bacteria and did not show any activity against Gram-negative bacteria. These compounds were also evaluated for their effect on cell proliferation against three different cancer cell lines using MTT assay. All the compounds inhibited cell proliferations less than or close to 50% when tested at a final concentration of 10μM.

Introduction

Hydrazines and its derivatives are important synthetic building blocks for various heterocyclic compounds. These compounds are receiving renewed interest because of the recent discovery of their remarkable biological activities as drugs, pesticides and amino acid precursors [1]. Substituted hydrazines are key components of azapeptides, a type of peptidomimetics, in which one or more of the amino acid residues have been replaced by monomers with N in the position of chiral carbons. Hydrazine based peptidomimetics are found to be potent agents against hepatitis, AIDS and SARS [2-3]. Thiazole moiety is a

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prevalent scaffold in a number of naturally occurring and synthetic molecules with attractive biological activities such as antitubercular, anticancer, antibacterial, antifungal, antiviral, anti*candida*, cytotoxic, anticonvulsant, antiparkinsonian and anti-inflammatory activities [4-17]. Pyrimidines represent a broad class of compounds, which have received considerable attention due to their wide range of biological activities [18]. Several pyrimidines have been reported as antihypertensive, anti-inflammatory, anticancer agents and COX-2 inhibitors [19-21]. Wang *et al* reported some pyrimidines substituted with thiazole nucleus as CDK inhibitors [22]. These observations prompted us to undertake synthesis and evaluation of biological activities of novel *N*,*N*'-disubstituted hydrazines by incorporating the two moieties i.e., thiazole and pyrimidine on hydrazine so as to obtain better biologically active agents.

A large number of methods are reported in the literature for the synthesis of thiazole nucleus [23]. These methods are primarily based on either the well known Hantzsch's thiazole synthesis [23a], which involves the use of highly toxic and lachrymatory α-haloketones, or a few other methods which suffer from other drawbacks. [Hydroxy(tosyloxy)iodo]benzene (HTIB) commonly known as Koser's reagent is the sole efficient reagent for inducing α-tosyloxylation of enolisable ketones [24]. The resulting α-tosyloxyketones are environmentally benign alternatives to the toxic and lachrymatory α-haloketones. Since it is generally not necessary to isolate the α-tosyloxyketones, they can be utilised *in situ* as strategic precursors for the one-pot synthesis of a wide range of heterocycles [25]. Keeping this in mind and as a part of our ongoing comprehensive programme to explore the utility of HTIB in the synthesis of a wide variety of heterocyclic compounds possessing various biological activities, we herein report an efficient HTIB mediated method for the synthesis of some novel *N*,*N*'-disubstituted hydrazines as antibacterial and cytotoxic agents. The procedure is facile and avoids the use of highly toxic and hazardous reagents.

Experimental

Materials and methods

Melting points were determined in open capillaries in electrical apparatus and are uncorrected. Infrared spectra were recorded on IR M-500 spectrophotometer (Buck Scientific Inc, Norwalk, CT) in KBr pellets (ν_{max} in cm^{-1}). ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on a Bruker instrument (Billerica, MA) by using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as δ in ppm. Coupling constants (J) are given in Hertz (Hz). Mass spectra and elemental analysis were performed at SAIF, CDRI, Lucknow and the compounds gave satisfactory results (within ± 0.05 of the calculated values).

2-Hydrazino-4,6-dimethylpyrimidine was prepared by following a method already reported in the literature [26].

Synthesis of *N*-(4,6-dimethylpyrimidin-2-yl)thiosemicarbazide (2)

2-Hydrazino-4,6-dimethylpyrimidine **1** (1.38 g, 10 mmol) was dissolved in ethanol and ammonium thiocyanate (1.9 g, 25 mmol) was added to it followed by 5 ml 9N HCl. Then the resulting solution was allowed to reflux for about 8 hours. Reaction was monitored by TLC. After completion of the reaction, the solution was allowed to concentrate and then cooled. The solid thus obtained was filtered, neutralized with aq. $NaHCO_3$ solution and washed with water.

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Recrystallization from ethanol afforded *N*-(4,6-dimethylpyrimidin-2-yl)thiosemicarbazide **2.**

Yield: 72%, mp (°C): 220-222. IR (KBr, cm^{-1}): 3369, 3323, 3262, 3174, 1644, 1608, 1594; ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.24 (s, 6H, C_4-CH_3, C_6-CH_3, Py), 6.62 (s, C_5-H, Py), 7.22 (brs, 1H, -NH), 7.66 (brs, 1H, -NH), 8.78 (brs, 1H, -NH), 9.20 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 23.90, 112.40, 162.83, 167.64, 182.58. Anal. Calcd for $C_7H_{11}N_5S$: C, 42.62; H, 5.62; N, 35.50. Found: C, 42.60; H, 5.64; N, 35.52. ESI-MS: *m/z* 198.05 $(M+H)^+$.

General procedure for the synthesis of *N*-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-arylthiazol-2-yl)hydrazines 4a-h

To a solution of an appropriate methyl ketone (1 mmol) in acetonitrile, HTIB (0.402 g, 1 mmol) was added and the resulting reaction mixture was refluxed for 2 h. When formation of α-tosyloxyketone **3** was indicated by the TLC, a solution of *N*-(4,6-dimethylpyrimidin-2-yl)thiosemicarbazide **2** (0.197 g, 1 mmol) in acetonitrile was added to the reaction mixture. The contents were allowed to stir at room temperature for another 6 h. Reaction was monitored by TLC. After completion of the reaction, a solid separated out which was filtered, neutralized with aq. $NaHCO_3$ and washed with water. The product was recrystallized with ethanol to give pure *N*-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-arylthiazol-2-yl)hydrazines **4a-h.**

N-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-phenylthiazol-2-yl)hydrazine **(4a)**

Yield: 75%, mp (°C): 240-242. IR (KBr, cm^{-1}): 3186, 3117, 1597, 1558, 1443. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.24 (s, 6H, C_4-CH_3, C_6-CH_3, Py), 6.61 (s, C_5-H, Py), 7.14 (s, 1H ,C_5-H, Th), 7.27-7.30 (m, 1H, C_4-H, Ph), 7.36-7.41 (m, 2H, C_3-H, C_5-H, Ph), 7.83 (d, 2H, *J*=7.8 Hz, C_2-H, C_6-H, Ph), 9.25 (brs, 1H, -NH), 9.46 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 174.70, 167.87, 163.24, 151.24, 135.34, 129.00, 127.83, 125.97, 112.37, 102.79, 23.90. Anal. Calcd for $C_{15}H_{15}N_5S$: C, 60.58; H, 5.08; N, 23.55. Found: C, 60.57; H, 5.09; N, 23.56. ESI-MS: *m/z* 298.13$(M+H)^+$.

N-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-chlorophenylthiazol-2-yl)hydrazine **(4b)**

Yield: 72%, mp (°C): 230-232. IR (KBr, cm^{-1}): 3209, 3024, 1597, 1558. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.24 (s, 6H, C_4-CH_3, C_6-CH_3, Py), 6.61 (s, 1H, C_5-H, Py), 7.21 (s, 1H, C_5-H, Th), 7.44 (d, 2H, *J*=8.4Hz, C_3-H, C_5-H, Ar), 7.85 (d, 2H, *J*=8.4Hz, C_2-H, C_6-H, Ar), 9.28 (brs, 1H, -NH), 9.52 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 174.89, 167.87, 163.26, 150.00, 134.20, 132.21, 128.99, 127.68, 112.40, 103.55, 23.90. Anal. Calcd for $C_{15}H_{14}ClN_5S$: C, 54.29; H, 4.25; N, 21.11. Found: C, 54.28; H, 4.25; N, 21.09. ESI-MS: *m/z* 332.13 $(M+H)^+$ / 334.12 $(M+H+2)^+$ (3:1).

N-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-fluorophenylthiazol-2-yl)hydrazine **(4c)**

Yield: 78%, mp (°C)**:** 236-238. IR (KBr, cm^{-1}): 3209, 3016, 1605, 1558. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.24 (s, 6H, C_4-CH_3, C_6-CH_3, Py), 6.60 (s, C_5-H, Py), 7.12 (s, 1H ,C_5-H, Th), 7.18- 7.24 (m, 2H, C_3-H, C_5-H, Ar), 7.84-7.89 (m, 2H, C_2-H, C_6-H, Ar), 9.28 (brs, 1H, -NH), 9.50 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 174.86, 167.89, 163.58, 163.25, 150.19, 131.97, 127.99, 115.94, 112.40, 102.50, 23.88. Anal. Calcd for $C_{15}H_{14}FN_5S$: C, 57.13; H, 4.47; N, 22.21. Found: C, 57.15; H, 4.46; N, 22.22. ESI-MS: *m/z* 316.14 $(M+H)^+$.

N-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-bromophenylthiazol-2-yl)hydrazine **(4d)**

Yield: 74%, mp (°C): 228-230. IR (KBr, cm^{-1}): 3217, 3024, 1597, 1558. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.24 (s, 6H, C_4-CH_3, C_6-CH_3, Py), 6.61 (s, C_5-H, Py), 7.22 (s, 1H, $C_{5'}$-H, Th), 7.57 (d, 2H, *J*=8.7 Hz, C_3-H, C_5-H, Ar), 7.78 (d, 2H, *J*=8.7 Hz, C_2-H, C_6-H,

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Ar), 9.27 (brs, 1H, -NH), 9.52 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 174.90, 167.91, 163.23, 150.03, 134.51, 131.91, 128.00, 120.79, 112.44, 103.67, 23.90. Anal. Calcd for $C_{15}H_{14}BrN_5S$: C, 47.88; H, 3.75; N, 18.61. Found: C, 47.87; H, 3.76; N, 18.60. ESI-MS: *m/z* 376.05 $(M+H)^+$ / 378.04 $(M+H+2)^+$ (1:1).

N-(4,6-dimethylpyrimidin-2-yl)-*N′*(4-tolylthiazol-2-yl)hydrazine **(4e)**

Yield: 76%, mp (°C): 210-212. IR (KBr, cm^{-1}): 3424, 3219, 1602, 1567. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.33 (s, 6H, C_4-CH_3, C_6-CH_3, Py), 2.35 (s, 3H, C_4-CH_3, Ar), 6.53 (s, 1H, C_5-H, Py), 6.77 (s, C_5-H, Th), 7.17 (d, 2H, *J*=8Hz, C_3-H, C_5-H, Ar), 7.69 (d, 2H, *J*=8Hz, C_2-H, C_6-H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 168.35, 162.46, 158.35, 146.78, 146.43, 132.23, 129.23, 125.91, 113.40, 103.02, 23.85, 21.23. Anal. Calcd for $C_{16}H_{17}N_5S$: C, 61.71; H, 5.50; N, 22.49. Found: C, 61.70; H, 5.50; N, 22.48. ESI-MS: *m/z* 312.12 $(M+H)^+$.

N-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-methoxyphenylthiazol-2-yl)hydrazine **(4f)**

Yield: 78%, mp (°C): 198-200. IR (KBr, cm^{-1}): 3178, 3109, 1597, 1558. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.36 (s, 6H, C_4-CH_3, C_6-CH_3), 3.85 (s, 3H, C_4-OCH_3, Ar), 6.57 (s, C_5-H, Py), 6.73 (s, C_5-H, Th), 6.93 (d, *J*=8.7Hz, 2H, C_3-H, C_5-H, Ar), 7.77 (d, *J*=8.7Hz, C_2-H, C_6-H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 174.70, 168.35, 159.26, 151.97, 147.94, 127.95, 127.28, 113.90, 113.35, 101.95, 55.30, 23.88. Anal. Calcd for $C_{16}H_{17}N_5OS$: C, 58.70; H, 5.23; N, 21.39. Found: C, 58.71; H, 5.21; N, 21.38. ESI-MS: *m/z* 328.12 $(M+H)^+$;

N-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-nitrophenylthiazol-2-yl)hydrazine **(4g)**

Yield: 68%, mp (°C): 186-188. IR (KBr, cm^{-1}): 3310, 3209, 1597, 1558, 1512, 1342. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.25 (s, 6H, C_4-CH_3, C_6-CH_3, Py), 6.63 (s, C_5-H, Py), 7.54 (s, C_5-H, Th), 8.08 (d, *J*=8.4Hz, 2H, C_2-H, C_6-H, Ar), 8.26 (d, *J*=8.4Hz, 2H, C_3-H, C_5-H, Ar), 9.32 (brs, 1H, -NH), 9.65 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 175.12, 167.93, 163.14, 149.20, 146.56, 141.30, 126.76, 124.52, 112.53, 107.74, 23.88. Anal. Calcd for $C_{15}H_{14}N_6O_2S$: C, 52.62; H, 4.12; N, 24.55. Found: C, 52.63; H, 4.10; N, 24.55. ESI-MS: *m/z* 343.12 $(M+H)^+$.

N-(4,6-dimethylpyrimidin-2-yl)-N′-(4-(2)-thienylthiazol-2-yl)hydrazine **(4h)**

Yield: 65%, mp (°C): 172-174. IR (KBr, cm^{-1}): 3186, 3078, 1597, 1558. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.24(s, 6H, C_4-CH_3, C_6-CH_3, Py), 6.61 (s, C_5-H, Py), 6.97 (s, C_5-H, Th), 7.05-7.07 (m, 1H, C_4-H, thienyl), 7.41-7.44 (m, 2H, C_3-H, C_5-H, thienyl), 9.27 (brs, 1H, -NH), 9.56 (brs, 1H, -NH). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 174.82, 167.88, 163.20, 145.93, 139.58, 128.28, 125.36, 123.49, 112.42, 101.14, 23.91. Anal. Calcd for $C_{13}H_{13}N_5S_2$: C, 51.46; H, 4.32; N, 23.08. Found: C, 51.48; H, 4.31; N, 23.07. ESI-MS: *m/z* 304.08 $(M+H)^+$

Biological Testing

Test microorganisms

Total four microbial strains were selected on the basis of their clinical importance in causing diseases in humans. All the synthesized compounds **4a-h** were screened for evaluation of antibacterial activity against two Gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Bacillus subtilis* MTCC 121) and two Gram-negative bacteria (*Escherichia coli* MTCC 1652 and *Pseudomonas aeruginosa* MTCC 741). The bacteria were subcultured on Nutrient agar.

Antibacterial activity

The antibacterial activity of all the compounds was evaluated by the agar well

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diffusion method. All the bacterial cultures were adjusted to 0.5 McFarland standard, which is visually comparable to a microbial suspension of approximately 1.5 $\times 10^8$ cfu/ml. 20 ml of agar medium was poured into each Petri plate and plates were swabbed with 100 µl inocula of the test microorganisms and kept for 15 min for adsorption. Using sterile cork borer of 8 mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 µl volume with concentration of 4.0 mg/ml of each compound reconstituted in the dimethylsulphoxide (DMSO). All the plates were incubated at 37 °C for 24 hrs. Antibacterial activity of each compound was evaluated by measuring the zone of growth inhibition against the test organisms with zone reader (HiAntibiotic zone scale). DMSO was used as a negative control whereas Ciprofloxacin was used as positive control for bacteria. This procedure was performed in three replicate plates for each organism.

Determination of Minimum Inhibitory Concentration (MIC) of chemical compounds

MIC is the lowest concentration of an antimicrobial compound that will inhibit the visible growth of a microorganism after overnight incubation**.** MIC of the various compounds against bacterial strains was tested through a modified agar well diffusion method. In this method, a two-fold serial dilution of each chemically synthesized compound was prepared by first reconstituting the compound in DMSO followed by dilution in sterile distilled water to achieve a decreasing concentration range of 512 to 1 µg/ml. A 100 µl volume of each dilution was introduced into wells (in triplicate) in the agar plates already seeded with 100 µl of standardized inoculum (10^6 cfu/ml) of the test microbial strain. All test plates were incubated aerobically at 37 °C for 24 h and observed for the inhibition zones. MIC, taken as the lowest concentration of the chemical compound that completely inhibited the growth of the microbe, showed by a clear zone of inhibition, was recorded for each test organism. Ciprofloxacin was used as positive control while DMSO as negative control.

Cell Culture:

HCT-116 (colon cancer cell line) and BT-474 (breast cancer cell line) were cultured in DMEM supplemented with 10% fetal serum albumin and 50 µg/ml of penicillin and streptomycin. JURKAT (immune system cancer cell line) were cultured in RPMI supplemented with 10% fetal serum albumin and 50 µg/ml of penicillin and streptomycin. All cell lines were maintained in an incubator containing 5% CO_2 at 37 °C.

Cell Viability Assay

Cells were seeded in a 96-well plate at a density of 7500/ml and grown overnight. Cells were treated with various compounds at a final concentration of 10 µM and incubated for 48 h. Cell viability assay was performed using a MTT cell proliferation kit from ATCC. In summary, 10 µl MTT reagent was added to each well, and cells were placed back in incubator for 4 hours. 100 µl of detergent (from kit) was added and absorbance data was collected at 570 nm using Biotek synergy 2 spectrophotometer,
Data was calculated as percentatge of cell survival using the following formula;
% cell survival = (100/At*As)
Where At and As are the absorbance of wells treated with test compounds and solvent control, respectively.

Results and Discussion

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Chemistry

In the present study, synthesis of *N*-(4,6-dimethylpyrimidin-2-yl)-*N*′-(4-arylthiazol-2-yl)hydrazines **4a-h** was carried out by treating *N*-(4,6-dimethylpyrimidin-2-yl)thiosemicarbazide **2** with *α*-tosyloxy ketones **3a-h** which, in turn, have been generated *in situ* by the reaction of methyl ketones with [hydroxy(tosyloxy)iodo]benzene, HTIB in acetonitrile (**Scheme 1**). The key intermediate, *N*-(4,6-dimethylpyrimidin-2-yl)thiosemicarbazide **2**, has been synthesized by the reaction of 2-hydrazino-4,6-dimethylpyrimidine **1** with ammonium thiocyanate in refluxing ethanol in the presence of conc. HCl. All the new compounds were characterized by their spectral data (IR, ^{1}H NMR, ^{13}C NMR, mass) and elemental analyses.

Scheme 1. Synthesis of *N*-(4,6-dimethylpyrimidin-2-yl)-*N*′-(4-arylthiazol-2-yl)hydrazines **4a-h**

In the IR spectrum of **2**, four absorption bands appeared at 3174, 3262, 3323 & 3369 cm^{-1} due to N-H stretchings and one absorption band at 1608 cm^{-1} indicating C=S stretch. The ^{1}H NMR spectrum of **2** displayed one singlet of six proton intensity at δ 2.25 ppm corresponding to C_4-CH_3 and C_6-CH_3 of pyrimidine nucleus and another singlet of one proton intensity at δ 6.62 ppm corresponding to pyrimidine 5-H. Compound **2** also exhibited four broad signals each of one proton intensity at about δ 7.2, 7.6, 8.7 & 9.2 ppm which are exchangeable with D_2O indicating the presence of two thiocarboxamide ($CSNH_2$) protons and two NH protons, respectively. Further support for the structure **2** was provided by ^{13}C NMR spectrum which exhibited signals at δ 23.90 ppm corresponding to C_4 and C_6-CH_3. Also signal at about δ 182.58 ppm in ^{13}C NMR spectrum demonstrate the presence of C=S group [27]. The IR spectrum of **4a** revealed two characteristic absorption bands for N-H stretch at 3186 and 3117 cm^{-1}. The ^{1}H NMR spectra of **4a** displayed two singlets of one proton intensity each at δ 6.61 and δ 7.14 ppm due to the protons corresponding to pyrimidine 5-H [22] and thiazole 5-H, [9,11] respectively. And one more singlet of six proton intensity has also been observed at δ 2.33 ppm corresponding to C_4-CH_3 and C_6-CH_3 of pyrimidine nucleus. In the ^{13}C NMR spectra of **4a**, signals at about δ 112 & 103 ppm correspond to C_5 of pyrimidine [20] and C_5 of thiazole nuclei, respectively [27]. The detailed spectra of all the compounds have been given in experimental part.

Biological Testing

Antibacterial activity

The results of antibacterial activity have been summarized in **Table 1**. The observed minimum inhibitory concentrations (MIC) presented in **Table 2** were in accordance with the results obtained in the primary screening. All the tested compounds **4a-h**, possessed variable antibacterial activity against the Gram-positive bacteria while they did not exhibit any activity against Gram-negative bacteria. Compounds **4a**, **4b** and **4c** have shown good activity against *B. subtilis* (with MIC 64 μg/ml) and moderate activity against *S. aureus* (with MIC 128 μg/ml). Compounds **4d** and **4e** have also shown good activity against *B. subtilis* (with MIC 64 μg/ml) and slight activity against *S. aureus* (with MIC >128 μg/ml). Compounds **4f**, **4g** and **4h** are moderately active against *B. subtilis* and slightly active against *S. aureus*.

Inhibition of Cell proliferation

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The anti-proliferative effect of **4a-h** were determined at 10 μM final concentration in three different cancer cell lines as listed in the **Table 3** below. The compounds **4e, 4g** and **4h** were effective at causing little more than 50% inhibition of cell proliferation in HCT-116 while only **4e** and **4h** inhibited JURKAT cell proliferation more than 50%. The effect was not very drastic so compounds were not further investigated for determining IC50 values.

Conclusions

In summary, the present work describes a facile and efficient synthesis of some new *N*-(4,6-dimethylpyrimidin-2-yl)-*N′*-(4-arylthiazol-2-yl)hydrazines and their evaluation as antibacterial and cytotoxic agents.

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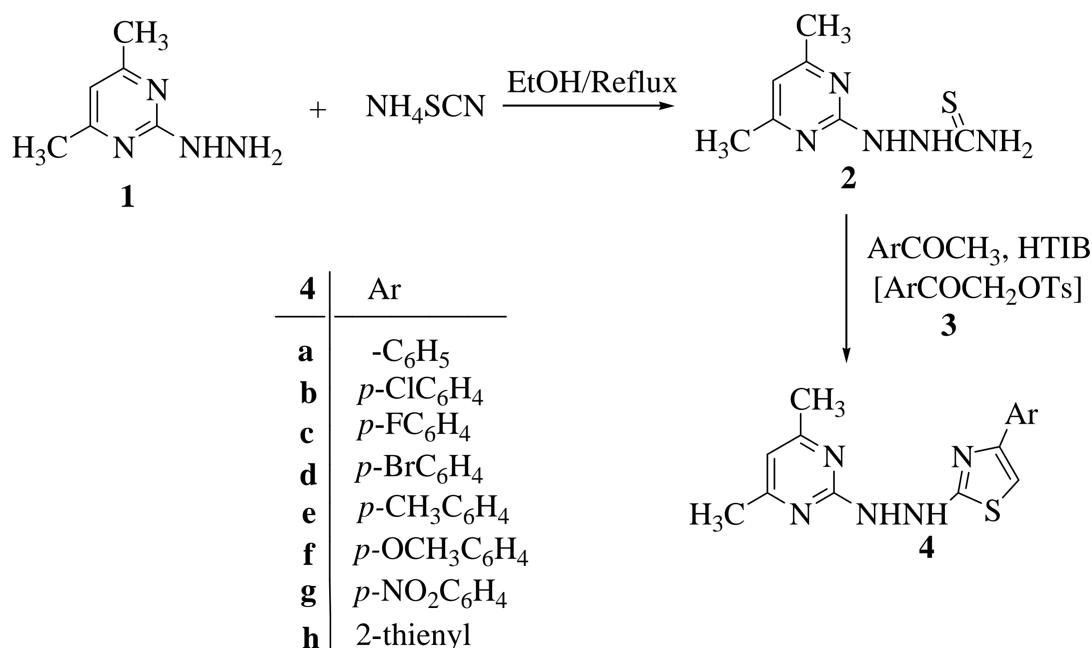

Scheme 1. Synthesis of *N*-(4,6-dimethylpyrimidin-2-yl)-*N′*(4-arylthiazol-2-yl)hydrazines **4a-h**

Table 1
In vitro antibacterial activity of **4a-h** by using agar diffusion assay technique

Compound	Diameter of zone of growth inhibition (mm)[a]			
	Gram-positive bacteria		Gram-negative bacteria	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*

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4a	16.6	19.3	-	-
4b	17.6	19.6	-	-
4c	16.0	19.6	-	-
4d	14.6	18.3	-	-
4e	15.6	18.3	-	-
4f	15.3	17.6	-	-
4g	15.3	17.6	-	-
4h	14.3	16.3	-	-
Ciprofloxacin	26.6	24.0	25.0	22.0

No activity;[a] Values, including diameter of the well (8mm), are means of three replicates

Table 2

MIC (µg/ml) values of compounds **4a-h** and reference drug against the respective microorganisms.

Organism	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	Ciprofloxacin
S. aureus	128	128	128	256	128	128	128	256	6.25
B.subtilis	64	64	64	64	64	128	128	128	6.25

Table 3

Anti-proliferative effect of compounds **4a-h**

Cancer Cell line	BT-474		HCT-116		JURKAT	
Samples	Average % cell survival	S.D.	Average % cell survival	S.D.	Average % cell survival	S.D.
Control	100.0	± 3.6	100.0	± 1.8	100.0	± 2.8
4a	72.3	± 7.3	108.9	± 10.8	66.7	± 3.5
4b	86.9	± 16.3	79.2	± 4.9	66.8	± 1.3
4c	104.0	± 9.0	57.4	± 1.6	75.0	11.5
4d	106.0	± 6.0	101.0	± 5.7	64.8	± 4.4
4e	78.8	± 4.8	47.3	± 1.6	46.5	± 10.5
4f	106.8	± 11.0	66.9	± 2.9	62.2	± 0.4
4g	83.1	± 2.0	44.9	± 0.4	72.2	± 6.1
4h	84.1	± 2.4	39.7	± 10.6	38.3	± 2.0
Doxo	13.7	± 2.6	12.1	± 2.0	13.0	± 2.0

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