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Synthesis, spectral characterization and antimicrobial studies of novel s-triazine derivatives

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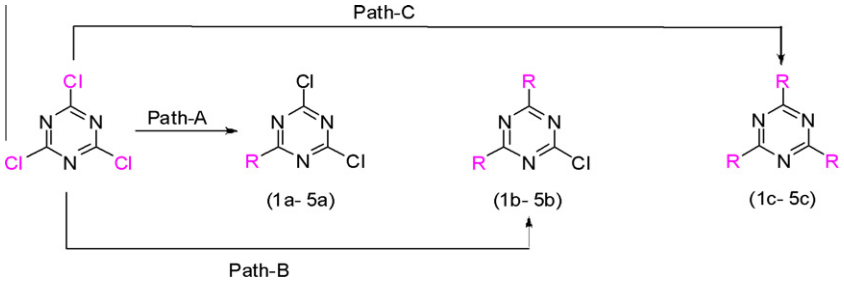
HIGHLIGHTS

- Series of novel hybrids s-triazine derivatives were synthesized and characterized.
- Formation of the novel hybrids were confirmed by 1D, 2D NMR and HR-MS spectroscopy.
- Excellent and moderate antimicrobial activities were observed.

GRAPHICAL ABSTRACT



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ABSTRACT

A series of fifteen novel triazinyl derivatives, with various natural nucleobases by mono, di and tri substitution in cyanuric chloride at the 2,4- and/or 6-positions was synthesized. Target molecules were synthesized by stoichiometric addition of various nucleophiles to cyanuric chloride in the presence of suitable base. The structural characterizations of all the compounds were made by spectral and analytical techniques, IR, ^{1}H NMR, ^{13}C NMR, and 2D NMR (HSQC, HMBC), mass spectral and elemental analysis. All the synthesized compounds were screened for *in vitro* antimicrobial activity against a panel of selected bacterial and fungal strains using Streptomycin and Amphotericin B as standards. The minimum inhibition concentration (MIC) results revealed that most of the purine (**1a–2a**, **1b–2b**, and **1c–2c**) compounds exhibit excellent activity against selected bacterial and fungal strains.

Introduction

Microbes including bacteria and fungi cause severe life threatening infections such as pneumonia and surgical wound infections. Development and spread of multi-drug resistant strains of bacteria and fungi pose a public health hazard worldwide. Purines (adenine, guanine) and pyrimidines (cytosine, thymine, uracil) are important groups of heterocyclic compounds in the field of medicinal chemistry. In recent decades, more number of purine and pyrimidine compounds have been screened for a wide variety of biological targets than the other heterocycles [1–3]. Thioguanine, 5-fluorouracil, vidarabine, acyclovir, carbovir are some of the purine and pyrimidine based therapeutic drugs are extensively used for the clinical purposes. Most of these drugs were discovered through cytotoxic screening followed by mechanistic studies. A close relationship was observed between many newly introduced anticancer agents and DNA strand scission process [4]. 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) has been largely used as a starting material due to the ease of displacement of chlorine atoms by various nucleophiles. 1,3,5-triazine compounds possess potent antiprotozoal [5] anticancer [6,7], antimalarial [8], antiviral [9] and antimicrobial activity [10]. In addition 1,3,5-triazine compounds have been used in the treatment of depression [11] and hence received a consider-

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able therapeutic importance [12–17]. The target molecules were synthesized by successive substitution of nucleophiles with the selective and sequential replacement of three chlorine atom [18] in the presence of triethylamine (TEA) base. Beata Kolesinska and Kaminski showed [19] that the reactivity may be enhanced manifold by using mild base tertiary amines. The umpolung of substituent effect in nucleophilic aromatic substitution enabled them to synthesize tri-substituted s-triazine derivatives as mono, di and tri-substituted symmetrical and unsymmetrical derivatives of cyanuric chloride under mild conditions [20]. Recently, cyanuric chloride is given an importance in the synthetic and medicinal field due to their reactivity towards C—Cl, to C—N [19,21], C—O [7,22], and C—C [23] and their bond formation with various nucleophiles. There is no report in the literature regarding the synthesis of s-triazinyl derivatives with various nucleobases (adenine, guanine, cytosine, thymine and uracil). As an inception, various s-triazine based nucleobases were synthesized and characterized by FT-IR, 1D NMR (^{1}H, ^{13}C), 2D NMR (HSQC, HMBC), mass (HRMS), CHN analysis and the antimicrobial activities were screened.

Experimental

Characterization techniques

Melting points (mps) were recorded on open capillary melting point apparatus and are uncorrected. IR spectra were obtained by Jasco FTS 3000MX (KBr pellets). ^{1}H NMR spectra were recorded with a Bruker AVANCE III 500 MHz spectrometer at room temperature, using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 125.76 MHz and are referenced using the central line of the solvent signal (DMSO-d_6 septet at δ = 39.5 ppm). Mass spectra were recorded with JOEL GCMATE II instrument. Elemental analyses (C, H and N) were performed with a Perkin Elmer 2400 Series II CHN Analyzer. Column chromatography was carried out on (Fluka) silica gel 60 (100–200 or 200–400 mesh). TLC (Silica gel) was performed on silica gel coated (Merk Kiesel 60 GF-254, 0.2 mm thickness) sheets. All reagents and solvents were commercially obtained (Sigma–Aldrich®, Himedia®) and used directly without further purification.

Synthesis

*General procedure for synthesis of compounds (**1a–c**, **3a–c**, **4a–c** and **5a–c**): (Paths A, B and C)*

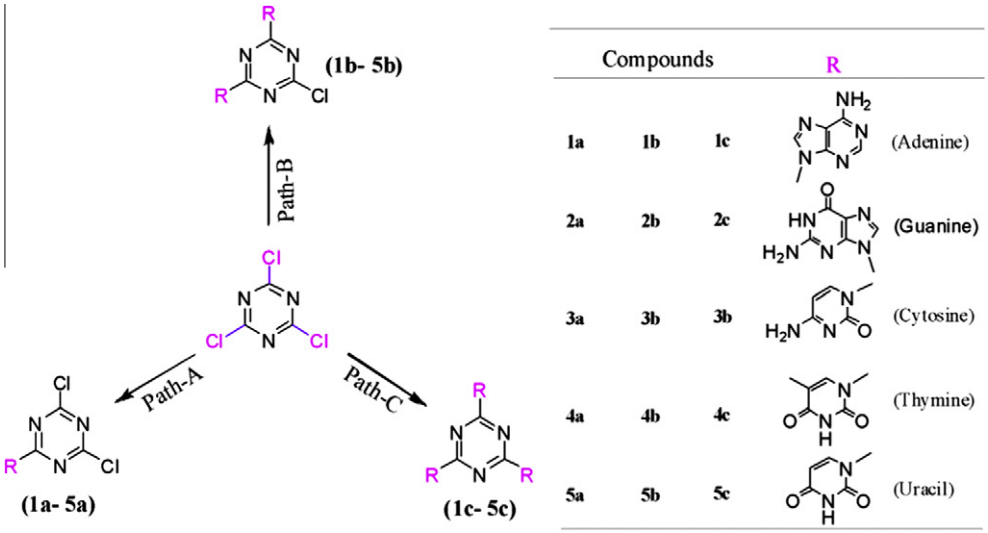
Cyanuric chloride (0.422 g, 0.25 mmole) in Tetrahydrofuran (25 mL), TEA (0.1 mmole) and adenine (0.28 g, 0.25 mmole) in water (25 mL) were placed into a 250 mL two neck round bottom flask which was fitted with reflux condenser and thermometer. The reaction mixture was refluxed at 80 °C for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The product formed was washed with water and THF (2:1) mixture. The crude was further purified by column chromatography with the eluent dichloromethane and chloroform (9:1) mixture (Scheme 1).

*9-(4,6-dichloro-1,3,5-trizin-2-yl)-9H-purin-6-amine (**1a**).* Yield 71%; Light green yellow solid; mp > 265 °C (dec); FT-IR (KBr): ν_{max} 3348, 2923, 2838, 1569, 1474, 1405, 1297, 1208, 1052, 1027, 939, and 649 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.11 (s, 1H), 8.08 (s, 1H), 7.13 (s, 2H, NH_2); ^{13}C NMR (125.76 MHz, DMSO-d_6): δ (ppm) 155.0, 151.7, 151.5, 150.4, 140.4, 138.1, and 117.1; HRMS (m/z) 283.24 ($M + H^+$); Anal. Calcd. for $C_6H_4Cl_2N_8$: C, 33.94; H, 1.46; and N, 39.06; and Found: C, 34.01; H, 1.50; and N, 38.99%.

*Preparation procedure for compounds (**2a–2c**)*

A mixture of cyanuric chloride (0.422 g, 0.25 mmole) in tetrahydrofuran (25 mL), guanine (0.34 g, 0.25 mmole) in dimethyl sulfoxide and K_2CO_3 (0.1 mmole) were placed into a 250 mL two neck round bottom flask fitted with condenser and thermometer (Scheme 1). The reaction mixture was refluxed at 80 °C for 16 h. The progress of the reaction was monitored by TLC. After the completion of the reaction whole mixture was cooled to room temperature. All the solvents were removed by applying vacuum and the crude product was washed with THF (25 mL). The crude obtained was filtered and crystallized with the dimethyl sulfoxide (DMSO).

*2-amino-9-(4,6-dichloro-1,3,5-triazin-2-yl)-1H-purin-6(9H)-one (**2a**).* Yield 62%; White solid; mp > 300 °C (dec); FT-IR (KBr): ν_{max} 3415, 3178, 3043, 2877, 2781, 1723, 1654, 1608, 1558, 1511, 1469, 1397, 1180, 1146, 1117, 1053, 837, 710, and 674 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 11.16 (s, 1H, NH), 8.94 (s,



Scheme 1. Reagents and conditions; **Path A** (**1a–5a**): Cyanuric chloride with (Adenine, guanine, cytosine, thymine and uracil) nucleobases (1:1 mol) Et_3N, THF, H_2O, reflux/80 °C for 4–16 h; **Path B** (**1b–5b**): Cyanuric chloride and nucleobases (1:2 mol) Et_3N, THF, H_2O, reflux/90 °C for 7–21 h; and **Path C** (**1c–5c**): Cyanuric chloride and nucleobases (1:3 mol), Et_3N, THF, H_2O, reflux/90 °C for 20–29 h; for (**2a–2c**) the TEA replaced by K_2CO_3, THF, DMSO reflux/90 °C for 16–29 h.