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ORIGINAL ARTICLE

Synthesis of novel (*E*)-*N*′-(2-chloropyrimidin-4-yl)-*N*-(5-cyano-2-hydroxy-6-phenylpyrimidin-4-yl) formamidine derivatives and their antimicrobial activity

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Abstract A series of novel (*E*)-*N*′-(2-chloropyrimidin-4-yl)-*N*-(5-cyano-2-hydroxy-6-phenylpyrimidin-4-yl) formamidine derivatives were synthesized by the reaction of different aldehydes with 2-chloropyrimidin-4-amine and *in vitro* antimicrobial activity was evaluated. The synthesized compounds were characterized by elemental analyses, FT-IR, ^{1}H NMR and LC–MS spectral studies. Antimicrobial data revealed that among all the compounds screened, compounds **7l** and **7m** were found to have promising antimicrobial activity against all the selected pathogenic bacteria and fungi.

1. Introduction

Heterocyclic molecules are of biological interest due to their potential physical and chemical properties (Brown, 1998). Among these, the pyrimidine compounds occupy a unique position in pharmaceutical chemistry, as they are components of nucleic acids. Nucleosides are the most frequently used effective class of antiviral agents, with over twenty drugs currently approved for the treatment of viral diseases and a number of candidates in the clinical trials (Mansour and Storer 1997; Bergman et al., 2004). Consequently, the intense search for new nucleoside derivatives attracted extensive attention. Being bioactive molecules, pyrimidines are important components of the biological macromolecules, such as DNA and RNA. So introducing the pyrimidines into nucleoside derivatives may result in the discovery of a number of novel derivatives with potential antitumor and antiviral activities. The explosion of new approaches for their synthesis and most importantly, their selective synthesis is an interesting subject of organic and bioorganic chemistry.

The treatment of bacterial infections remains a challenging therapeutic problem because of emerging infectious diseases and the increasing number of multidrug-resistant microbial pathogens. Despite many antibiotics and chemotherapeutics available, the emergence of old and new antibiotic-resistant bacterial strains in the last decades leads to a substantial need

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for new classes of anti-bacterial agents (Inca et al., 2006). Pyrimidine and their derivatives are continuously attracting attention of the medicinal chemists in view of their profound range of biological activities, anti-HIV (Rawal et al., 2007), analgesic agents (Chhabria et al., 2007), antiproliferative (Schenone et al., 2008) and antitumor (Abbas et al., 2011). The pyrimidine nucleus has increasingly attracted the attention of synthetic chemists. Though the antimicrobial activity of pyrimidine derivatives has been extensively studied and well documented in the literature (Holla et al., 2006; Chambhare et al., 2003; Narayana et al., 2009), however, relatively few reports were available on the anti-inflammatory activity of the pyrimidine derivatives (Ramesh et al., 2010; Ballesteros et al., 1995; O'Hare et al., 2011; Shishoo et al., 1999; Papadakis and Targan, 2000). In connection with such studies, the present paper reported on the synthesis, antibacterial and antifungal activities of (*E*)-*N*′-(2-chloropyrimidin-4-yl)-*N*-(5-cyano-2-hydroxy-6-phenylpyrimidin-4-yl) formamidine derivatives **7a–n**.

2. Materials and methods

2.1. General

All solvents and reagents were purchased from Sigma Aldrich Chemicals. Melting points were determined on an electrically heated VMP-III melting point apparatus. The elemental analyses of the compounds were performed on a Perkin Elmer 2400 Elemental Analyzer. The FT-IR spectra were recorded using KBr discs on a FT-IR 4100 Infrared spectrophotometer. The NMR spectra were recorded using a Bruker DRX 400 spectrometer at 400 MHz for ^{1}H NMR with tetramethylsilane as the internal standard. Mass spectral data were obtained by LC/MSD Trap XCT. Silica gel for column chromatography was performed using Merck 7734 silica gel and Merck-made TLC plates. (*E*)-*N*′-(2-chloropyrimidin-4-yl)-*N*-(5-cyano-2-hydroxy-6-phenylpyrimidin-4-yl) formamidine derivatives **7a–n,** were prepared by the method summarized in Scheme 1.

2.2. Chemistry

2.2.1. General method for the synthesis of 4-amino-2-hydroxy-6-phenylpyrimidine-5-carbonitrile derivatives (*4a–n*)

The reaction of aromatic aldehyde **1a–n** (10 mmol), malononitrile (10 mmol) and phosphorus pentoxide (3.54 mmol) is stirred mechanically for 10 minutes in 25 ml absolute ethanol and then thiourea (20 mmol) is added and mixed thoroughly. The resulting reaction mixture was heated at reflux and it was poured on the crushed ice (about 200 gm) after the completion of the reaction monitored by TLC. The solid was filtered, washed with petroleum ether, dried and recrystallized by using ethanol.

2.2.2. General procedure for the synthesis of N-(5-cyano-2-hydroxy-6-phenylpyrimidin-4-yl) formamidine derivatives (*5a–n*)

A solution of compound **4a–n** (5.0 mmol) in formic acid (20 mL) was refluxed for 1 h. The solvent was evaporated and the residue was crystallized from ethanol to give compound **5a–n** in good yield.

2.2.3. General procedure for the synthesis of (*E*)-*N*′-(2-chloropyrimidin-4-yl)-*N*-(5-cyano-2-hydroxy-6-phenylpyrimidin-4-yl) formamidine derivatives (*7a–n*)

The Schiff base was prepared by reaction of equimole of **5a–n** and 2-chloropyrimidin-4-amine. Each reactant was dissolved in a minimum amount of ethanol, then mixed together and followed by addition of 2 ml glacial acetic acid. The solution was refluxed for 8 h then cooled to room temperature and poured into ice cold water. The solid product was collected through filtration and then dried using drying oven at 80 °C. The product was redissolved in ethanol for recrystallization and then dried to give a product.

*2.2.3.1. (E)-N′-(2-chloropyrimidin-4-yl)-N-(5-cyano-2-hydroxy-6-phenylpyrimidin-4-yl)formamidine (**7a**).* Recrystallization from ethanol afforded 80. FT-IR (KBr, cm^{-1}) *v*: 3560 (O–H), 3271 (N–H), 2220 (CN), 1697 (C=N). ^{1}H NMR (DMSO-d$_6$, 400 MHz) *δ*: 7.15–7.57 (m, 5H, Ar–H), 7.70–7.91 (d, 2H. Pyrimidine), 8.54 (s, 1H, N=CH), 8.93 (s, 1H, NH), 10.67 (bs, 1H, OH). MS (ESI) *m*/*z*: 352. Anal. Calcd. For $C_{16}H_{10}ClN_7O$ (in%): C, 54.63; H, 2.87; N, 27.87. Found. C, 54.61; H, 2.82; N, 27.95.

*2.2.3.2. (E)-N-(6-(4-chlorophenyl)-5-cyano-2-hydroxypyrimidin-4-yl)-N′-(2-chloropyrimidin-4-yl) formamidine (**7b**).* Recrystallization from ethanol afforded 82%. FT-IR (KBr, cm^{-1}) *v*: 3563 (O–H), 3276 (N–H), 2226 (CN), 1694 (C=N). ^{1}H NMR (DMSO-d$_6$, 400 MHz) *δ*: 7.31–7.51 (m, 4H, Ar–H), 7.72–7.93 (d, 2H. Pyrimidine), 8.52 (s, 1H N=CH), 8.92 (s, 1H NH), 10.67 (bs, 1H OH). MS (ESI) *m*/*z*: 386. Anal. Calcd. For $C_{16}H_9Cl_2N_7O$ (in%): C, 49.76; H, 2.35; N, 25.39. Found C, 49.71; H, 2.36; N, 25.32.

*2.2.3.3. (E)-N-(6-(4-bromophenyl)-5-cyano-2-hydroxypyrimidin-4-yl)-N′-(2-chloropyrimidin-4-yl) formamidine (**7c**).* Recrystallization from ethanol afforded 70%. FT-IR (KBr, cm^{-1}) *v*: 3566 (O–H), 3269 (N–H), 2219 (CN), 1690 (C=N). ^{1}H NMR (DMSO-d$_6$, 400 MHz) *δ*: 7.32–7.44 (m, 4H, Ar–H), 7.74–7.91 (d, 2H. Pyrimidine), 8.57 (s, 1H N=CH), 8.94 (s, 1H NH), 10.65 (bs, 1H OH). MS (ESI) *m*/*z*: 431. Anal. Calcd. For $C_{16}H_9BrClN_7O$ (in%): C, 44.62; H, 2.11; N, 22.77. Found C, 44.69; H, 2.15; N, 22.71.

*2.2.3.4. (E)-N′-(2-chloropyrimidin-4-yl)-N-(5-cyano-2-hydroxy-6-o-tolylpyrimidin-4-yl)formamidine (**7d**).* Recrystallization from ethanol afforded 78%. FT-IR (KBr, cm^{-1}) *v*: 3569 (O–H), 3271 (N–H), 2221 (CN), 1692 (C=N). ^{1}H NMR (DMSO-d$_6$, 400 MHz) *δ*: 2.50 (s, 3H, Ar–CH$_3$), 7.33–7.48 (m, 4H, Ar–H), 7.73–7.95 (d, 2H. Pyrimidine), 8.46 1H N=CH), (s, 8.95 (s, 1H NH), 10.67 (bs, 1H OH). MS (ESI) *m*/*z*: 366. Anal. Calcd. For $C_{17}H_{12}ClN_7O$ (in%): C, 55.82; H, 3.31; N, 26.81. Found C, 55.87; H, 3.36; N, 26.85.

*2.2.3.5. (E)-N-(6-(3-chlorophenyl)-5-cyano-2-hydroxypyrimidin-4-yl)-N′-(2-chloropyrimidin-4-yl) formamidine (**7e**).* Recrystallization from ethanol afforded 83%. FT-IR (KBr, cm^{-1}) *v*: 3560 (O–H), 3279 (N–H), 2218 (CN), 1695 (C=N). ^{1}H NMR (DMSO-d$_6$, 400 MHz) *δ*: 7.35–7.51 (m, 4H, Ar–H), 7.71–7.92 (d, 2H. Pyrimidine), 8.49 (s, 1H N=CH), 8.91 (s, 1H NH), 10.67 (bs, 1H OH). MS (ESI) *m*/*z*: 386. Anal. Calcd. For $C_{16}H_9Cl_2N_7O$ (in%): C, 49.76; H, 2.35; N, 25.39. Found C, 49.71; H, 2.38; N, 25.32.