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Synthesis, characterization, synergistic antimicrobial properties and molecular docking of sugar modified uridine derivatives

Jannatul MAOWA,[1] Asraful ALAM,[1] Kazi M. RANA,[1] Sujan DEY,[2] Anowar HOSEN,[3] Yuki FUJII,[4] Imtiaj HASAN,[5] Yasuhiro OZEKI,[6] and Sarkar M.A. KAWSAR[*1]

[1] *Department of Chemistry, Faculty of Science, University of Chittagong, Chittagong-4331, Bangladesh*
[2] *Department of Microbiology, Faculty of Biological Science, University of Chittagong, Chittagong-4331, Bangladesh*
[3] *Centre for Advanced Research in Sciences, University of Dhaka, Dhaka-1000, Bangladesh*
[4] *Department of Functional Morphology, Graduate School of Pharmaceutical Sciences, Nagasaki International University, 2825-7 Huis Ten Bosch, Sasebo, Nagasaki 859-3298, Japan*
[5] *Department of Biochemistry and Molecular Biology, Faculty of Science, Rajshahi University, Rajshahi-6205, Bangladesh*
[6] *Department of Life and Environmental System Science, School of Sciences, Yokohama City University, 22-2 Seto, Kanazawa-ku, Yokohama 236-0027, Japan*

Abstract. Nucleosides and their analogues are an important, well-established class of clinically useful medicinal agents that exhibit antiviral and anticancer activity. Thus, our research group has focused on the synthesis of new nucleoside derivatives that could be tested for their broad-spectrum biological activity. In this study, two new series of nucleoside derivatives were synthesized from uridine (**1**) through facile two-step reactions using the direct acylation method, affording 5'-*O*-acyl uridine derivatives in good yields. The isolated uridine analogs were further transformed into two series of 2',3'-di-*O*-acyl derivatives bearing a wide variety of functionalities in a single molecular framework to evaluate their antimicrobial activity. The new synthesized compounds were characterized through physicochemical, elemental and spectroscopic analysis, and all were screened for their *in vitro* antimicrobial activity against selected human and plant pathogenic strains. The test compounds revealed moderate to good antibacterial and antifungal activities and were more effective against fungal phytopathogens than against bacterial strains, while many of them exhibited better antimicrobial activity than standard antibiotics. Minimum inhibition concentration (MIC) and minimum bactericidal concentration (MBC) tests against all microorganisms were also conducted for five compounds based on their activity (**6**, **11**, **13**, **16**, and **17**). In addition, all the derivatives were optimized using density functional theory (DFT) B3LYP/6-31g+(d,p) calculations to elucidate their thermal and molecular orbital properties. A molecular docking study was performed using the human protein 5WS1 to predict their binding affinity and modes, and ADMET and SwissADME calculations confirmed the improved pharmacokinetic properties of the compounds. Besides, structure–activity relationship (SAR), thermogravimetric analysis (TGA), and X-ray diffraction (XRD) studies were also performed. Thus, the improvement of the bioactivity of these compounds is expected to significantly contribute to the design of more antimicrobial agents for therapeutic use in the future.

Keywords: ADMET; antimicrobial; molecular docking; synthesis; characterization; uridine.

[*] Corresponding author. *E-mail address*: akawsarabe@yahoo.com (Sarkar M.A. Kawsar)