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Synthesis and antimicrobial activity of some novel nucleoside analogues of adenosine and 1,3-dideazaadenosine

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Abstract—A number of nucleoside analogues have been synthesized and evaluated for their antibacterial and antifungal activities against *Staphylococcus aureus*, *Group D Streptococcus*, *Pseudomonas aeruginosa*, *Proteus* spp., *Salmonella* spp., *Aspergillus fumigatus*, *Penicillium marneffei*, *Candida albicans*, *Cryptococcus neoformans*, and *Mucor* spp. The compounds **1**, **4**, and **6** emerged as potent antibacterial agents with MIC values of 0.75, 0.38, and 0.19 μM, respectively, against *group D Streptococcus*. Further, the results suggest that the molecules **4**, **6**, and **7** would be potent antifungal agents as they show substantial degree of inhibition toward the growth of pathogenic fungi with MICs of 0.75, 0.38, and 0.38 μM, respectively.

The increasing prevalence of life-threatening fungal diseases and rapidly growing trend of antimicrobial resistance shown especially by Gram positive bacteria necessitate the development of new and more effective antimicrobial agents. Identification of novel antimicrobial drug with unique modes of action is desirable, since microbes resistant to available antimicrobial agents would unlikely be cross-resistant to these newer drugs.[1] The use of nucleoside analogues can be considered as a novel option as they are expected to act at genomic level, and thereby interfere with transcription or replication processes required for microbial survival. Since there are no alternative pathways in the pathogens for these basic metabolic processes, the nucleoside analogues, by inhibiting these basic pathways, can prove to be effective and better antimicrobial agents. Based on the diverse biological activity and chemical application of benzimidazole derivatives,[2–4] we set out to find a new class of drugs derived from benzimidazoles that may be targeted against major enzymes involved in the fungal and bacterial growth. All the newly synthesized analogues have structural similarity with the naturally occurring nucleoside, *S*-adenosylhomocysteine or SAH, which plays a key role in biological transmethylation reactions. SAH is removed by an enzyme SAH hydrolase,[5] and inhibition of this enzyme, in turn, causes feed back inhibition of biological transmethylation, resulting in the production of uncapped mRNAs and, as a result, less efficient translational process. So, targeting SAH hydrolase is useful in developing antifungal agents.[6–8] SAH is also a substrate for SAH nucleosidase found in bacterial methionine salvage pathway which catalyzes the conversion of methylthioadenosine into methylthioribose and adenine.[9] Targeting SAH nucleosidase may result in new antimicrobial agents and provide an alternative to the problem of resistance faced by most of the existing antibiotics. Further, since SAH nucleosidase is not found in humans, its inhibitors are expected to be non-toxic to human beings.

The compounds used in the present study are synthesized as shown in Scheme 1. For the synthesis of ribosides of 1,3-dideazaadenine (ii), 6-nitro-1,3-dideazaadenine, (iii) and 8-ethyl-1,3-dideazaadenine (iv), silylation of the corresponding substituted bases was performed using hexamethyldisilazane (HMDS) and trichloromethylsilane (TCS) in acetonitrile (CH_3CN) at its reflux point. Excess of HMDS and TCS was removed in vacuo after completion of the reaction. The resultant silyl derivatives were used, without further purification for coupling with suitably protected sugar, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (ABR). The coupling reactions were carried out in the presence of $SnCl_4$ as

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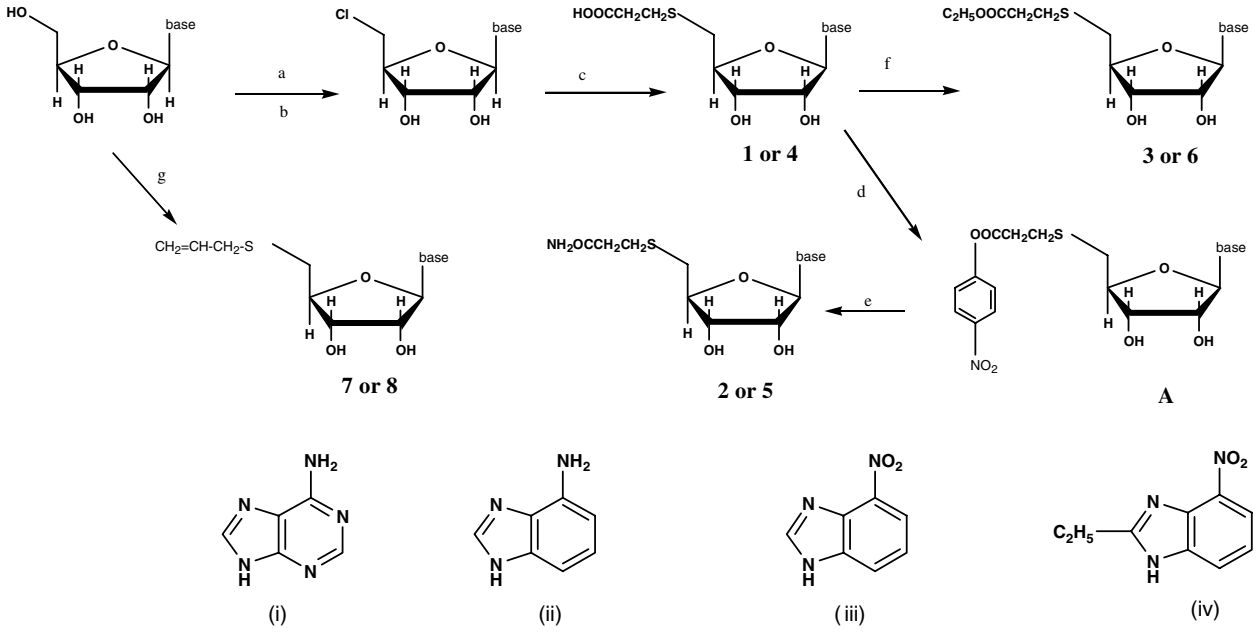

for 1-3, base = (i) adenine
for 4-6, base = (ii) 1,3-dideazaadenine
for 7, base = (iii) 6-nitro-1,3-dideazaadenine
for 8, base = (iv) 6-nitro-8-ethyl-1,3-dideazaadenine

Scheme 1. Reagents: (a) $SOCl_2$/HMPA, dry pyridine; (b) dowex (H^+), 2 N NH_4OH; (c) mercaptopropionic acid, DMAP/pyridine; (d) DCC, *p*-nitrophenol, dioxan; (e) NH_3; (f) DCC, EtOH, concd H_2SO_4; (g) allyl disulfide, triphenyl phosphine.

catalyst using Vorbrüggen and Bennua procedure.[10] The products were purified on silica gel column using DCM/MeOH and deprotected using ammonia (25%) for 5 h at 60 °C. The products were further washed several times with ether and recrystallized using aq ethanol. Adenosine and 9-(1′-β-D-ribofuranosyl) 1,3-dideazaadenine were converted to their 5′-chloro-5′-deoxy derivatives by treating them with thionyl chloride ($SOCl_2$) and hexamethylphosphoramide (HMPA).[11] 5′-Chloro-5′-deoxynucleosides were further treated with mercaptopropionic acid to give 5′-*S*-(propionic acid) 5′-deoxy-9-(1′-β-D-ribofuranosyl) adenine (**1**) and 5′-*S*-(propionic acid) 5′-deoxy-9-(1′-β-D-ribofuranosyl) 1,3-dideazaadenine (**4**), respectively. The –COOH function of **1** and **4** was activated by a reaction with *p*-nitrophenol and dicyclohexylcarbodiimide (DCC) in pyridine and triethylamine to get the corresponding activated ester **A**. The completion of the reaction was assessed by precipitation of dicyclohexylurea (DCU). The activated phenyl esters were then treated with ammonia to get the corresponding amides—5′-*S*-(propionamide) 5′-deoxy-9-(1′-β-D-ribofuranosyl) adenine (**2**) and 5′-*S*-(propionamide) 5′-deoxy-9-(1′-β-D-ribofuranosyl) 1,3-dideazaadenine (**5**). Compounds **1** and **4** when allowed to react with ethanol in the presence of DCC and catalytic amount of concd H_2SO_4 gave the esters-5′-*S*-(ethylpropionate) 5′deoxy-9-(1′-β-D-ribofuranosyl) adenine (**3**) and 5′-*S*-(ethylpropionate) 5′-deoxy-9-(1′-β-D-ribofuranosyl) 1,3-dideazaadenine (**6**), respectively. Similarly, glycosylation of 6-nitro-1,3-dideazaadenine (iii) and 8-ethyl-1,3-dideazaadenine (iv) with ABR gave their respective ribosides[12] which were further treated with allyl disulfide and triphenylphosphine to give **7** and **8**. This one step procedure is more convenient than the multistep procedure used earlier for 5′-sulfur generation and the yield is also considerably improved. The advantageous points of this reaction were high yield and absence of side reactions, such as the formation of cyclonucleoside, etc.[13]

All the compounds **1**–**8** were tested in vitro for antibacterial and antifungal activity[14] and they exhibited good to moderate activity against Gram positive bacteria and some human pathogenic fungi, Table 1. The positive results with compounds **1** and **4** against bacteria may be due to easy recognition of propionic acid by the bacterial cells as it is structurally similar to amino acids, the natural components of bacterial cell wall. Thus, the structural features of these molecules help in their better cellular uptake. In order to increase their effectiveness, compounds **1** and **4** were further converted into their derivatives, **3** and **6**, with biodegradable ester linkages. This modification is likely to have made the compounds more lipophilic in nature, which in turn may have made these molecules more effective inhibitors of enzymes involved in lipid and cell wall syntheses. The biodegradable ester linkage gets hydrolyzed inside the cell and the resulting carboxylate form of the drug molecule is thus entrapped inside, resulting in its higher bioavailability. The drug effect was better in its ester form, **6**, than its amide form, **5**, since ester bonds are easily hydrolyzed than amide bonds. The higher activity of these molecules against Gram positive bacteria than Gram negative bacteria might be due to the structural