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Amidine derived 1,3-diazabuta-1,3-dienes as potential antibacterial and antifungal agents

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Abstract—Several 1-aryl-2-phenyl-4-piperidino-4-thioalkyl-1,3-diazabuta-1,3-dienes were prepared by the treatment of *N*-arylimino isothiocyanate with piperidine followed by S-alkylation with alkyl iodides in the presence of dry acetone and potassium hydroxide. The constitution of the products was supported by IR, PMR and mass spectral study. The compounds synthesized were tested in in vitro against *E. coli*, *S. aureus*, *P. aeruginosa*, *B. cereus* and *B. subtilis* and fungal stains, *Candida albicans* and *Aspergillus niger*. Standard drugs were also tested under identical conditions for comparing the results.

1. Introduction

Antibiotic-resistant pathogens pose an enormous threat to the treatment of a wide range of serious infections.[1] Nosocomial and community-acquired agents have developed resistance to a wide range of antibiotics[2] and have proven to be highly successful in their ability to develop resistance mechanisms, often transferable, against virtually all commonly used antibiotics. The increasing number of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and most recently, Vancomycin-resistant enterococci (VRE) emphasize the need for new and alternative antimicrobial agents.[3] A structure-based approach to design potent and selective agents is an important component of the modern drug development process.[4–6] Pentamidine (Fig. 1) and berenil (Fig. 2) are aromatic diamidines that are known to bind to the DNA minor groove at AT tracts[1–10] and to have a long history as antimicrobial agents.[11] These molecules may be viewed as benzamidines connected by acyclic linkers. In the 1930s these type diamidine molecules were studied for their use against African trypanosomes.[12,13] A large number of

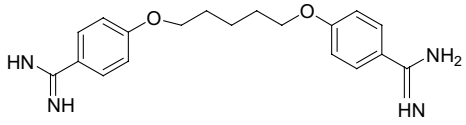

Figure 1. Pentamidine.

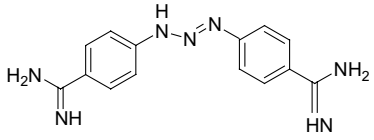

Figure 2. Berenil.

synthetic aromatic diamidines, which may be viewed as derived from 1 and 2 have demonstrated broad spectrum antimicrobial activity against several protozoan and fungal infections.[14] The interesting biological activities exhibited by amidines have prompted us to synthesize amidine derived, 1,3-diazabuta-1,3-dienes. As part of our efforts in the development of novel antibacterial agents, we have previously reported novel series of amidine derived 1,3-diazabuta-1,3-dienes for this purpose.[15,16] In this letter, we primarily focused on the introduction of a piperidine moiety at C-4 of

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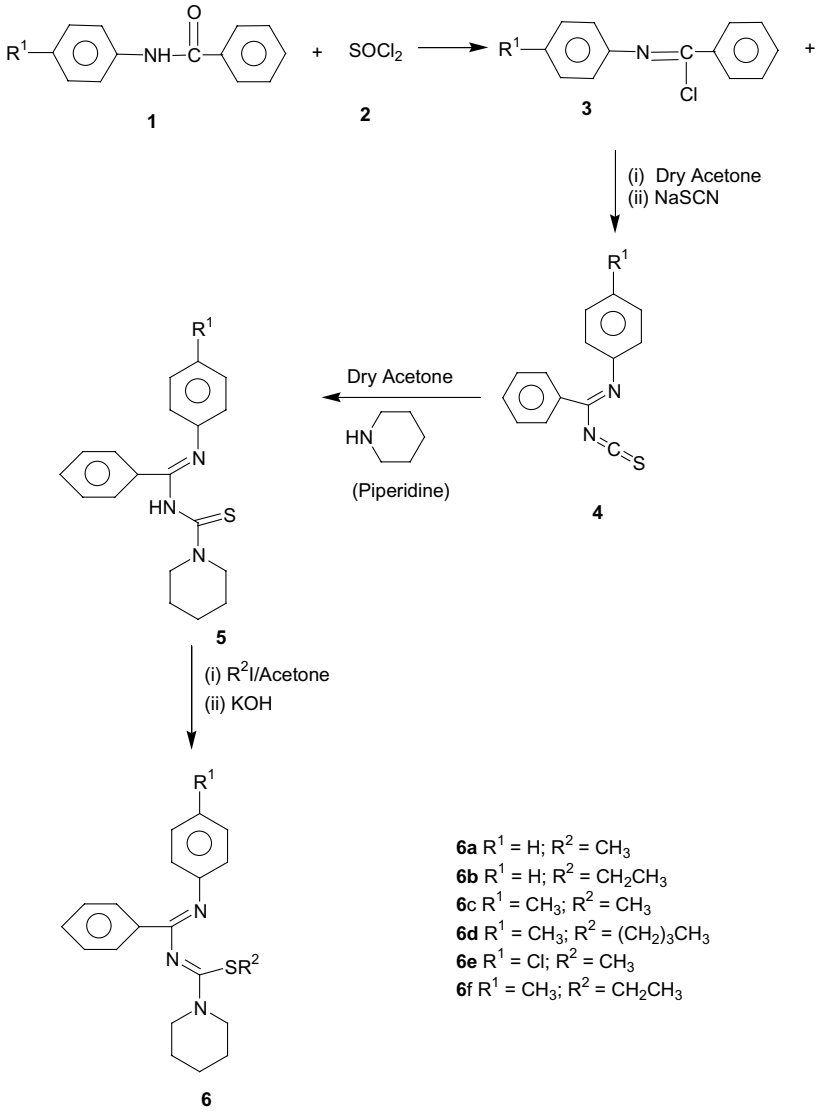
1,3-diazabuta-1,3-diene ring system and evaluate them for their antibacterial and antifungal activity.

2. Chemistry

A novel series of 1-aryl-2-phenyl-4-piperidino-4-thioalkyl-1,3-diazabuta-1,3-dienes was conveniently prepared[17,18] by the treatment of *N*-aryl imino isothiocyanates[19] **4** with secondary amine such as piperidine have been shown to result in very good yields of 4-[(α-arylamino) benzylidene thiocarbonyl)] secondary amines **5**, commonly referred to as thioureas. The alkylation of these thioureas with alkyl iodides viz. methyl iodide, ethyl iodide, butyl iodide and basification of the resultant hydroiodide salts with 3 N potassium hydroxide resulted in excellent yields of 1-aryl-2-phenyl-4-piperidino-4-thioalkyl-1,3-dizabuta-1,3-dienes **6** (Scheme 1). The 1,3-diazabuta-1,3-dienes so obtained (**6a**–**f**) were characterized on the basis of analytical data and spectral evidences.

3. Antimicrobial activity

The antibacterial activities of the synthesized compounds were determined by agar well diffusion method as recommended by the National Committee for Clinical Laboratory Standards,[20–22] at a concentration of 50 μg/mL using dimethyl sulfoxide (DMSO) as solvent against Gram positive microorganisms viz. *Bacillus subtilis* MTCC 121, *Bacillus cereus* MTCC 1272, *Staphyloccocus aureus* MTCC 1430 and Gram negative microorganisms such as *Escherichia coli* MTCC 42 and *Pseudomonas aeruginosa* MTCC 1034. Standard antibacterial Ciprofloxacin was also screened under similar conditions for comparison. While antifungal screening of the synthesized compounds was determined in a similar way using Czapek's agar medium at a concentration of 50 μg/mL against *Candida albicans* MTCC 183 and *Aspergillus niger* MTCC 404. Griseofulvin was used as standard antifungal drug and was subjected to the same screening pattern for comparison. Solvent control was maintained in both the studies under similar



Scheme 1. Synthesis of 1-aryl-2-phenyl-4-piperidino-4-thioalkyl-1,3-diazabuta-1,3-dienes.

Table 1. Antibacterial activity of compounds **6a–f** (zone of inhibition in mm[a])

Compound	*E. coli*	*S. aureus*	*P. aeruginosa*	*B. cereus*	*B. subtilis*
6a	+++	++	++	++	++
6b	+++	+++	++	+++	++
6c	+++	+++	++	++	++
6d	+++	+++	+++	++	++
6e	+++	++	+++	+	++
6f	+++	+	++	++	+++
Ciprofloxacin	+++	+++	++	++	+++
DMSO	–	–	–	–	–

[a] + (11–15 mm), ++ (16–20 mm), +++ (21–25 mm) and – (inactive).

Table 2. Antifungal activity of compound **6a–f** (zone of inhibition in mm[a])

Compound	*C. albicans*	*A. niger*
6a	–	–
6b	+	–
6c	–	–
6d	++	+
6e	+	+
6f	–	+
Griseofulvin	+++	+++
DMSO	–	–

[a] + (11–15 mm), ++ (16–20 mm), +++ (21–25 mm) and – (inactive).

conditions. The results were presented in Tables 1 and 2, respectively.

4. Results and discussion

It has been observed that some of these compounds exhibited interesting antibacterial activities. Results reveal that all the synthesized compounds were active against *E. coli* comparable to standard drug Ciprofloxacin. Compound **6a** showed maximum activity against gram positive *E. coli*, where as by the introduction of ethyl group in compound **6b**, increases its antibacterial activity against Gram positive and Gram negative bacterial strains. More over compound **6b** also shows significant antibacterial activity against *B. cereus*, which is greater than the standard drug as shown in Table 1. Compound **6c** was maximum active against *E. coli* and *S. aureus* whereas moderately active against other bacterial strains. Compound **6d**, which contains bulkier butyl group, shows maximum activity *E. coli*, *S. aureus* and *P. aeruginosa* and emerged out to be a one of potent antibacterial against Gram negative strains such as *E. coli* and *P. aeruginosa*. Introduction of chlorine in compound **6e** increases its antibacterial spectrum against Gram negative bacterial strains. Compound **6f** was maximum active against *E. coli* and *B. subtilis*. Solvent DMSO did not show any antibacterial activity. Therefore the results of antibacterial screening of compounds revealed that 1,3-diazabuta-1,3-dienes having a piperidino heterocycle showed significant activity comparable to standard drug against Gram positive and Gram negative bacterial strains. The other chemical moiety found to be favourable towards antibacterial activity was ethylthio followed by butylthio in the diazabuta-diene system.

The antifungal screening of the prepared 1,3-diazabuta-1,3-diene compounds revealed that piperidino moiety was not found to be favourable for antifungal activity. Compound **6a** and **6c** did not show any antifungal activity where as compound **6d** and **6e** was moderately active against *C. albicans* and *A. niger*. Compound **6b** and **6f** was moderately active against *C. albicans* and *A. niger*, respectively. It has been concluded that the antifungal activity displayed by the compounds **6a–f** were not comparable with the standard drug Griseofulvin.

Acknowledgements

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