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Design, synthesis and biological evaluation of 5-fluorouracil-derived benzimidazoles as novel type of potential antimicrobial agents

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ABSTRACT

A series of 5-fluorouracil benzimidazoles as novel type of potential antimicrobial agents were designed and synthesized for the first time. Bioactive assay manifested that some of the prepared compounds exhibited good or even stronger antibacterial and antifungal activities against the tested strains in comparison with reference drugs norfloxacin, chloromycin and fluconazole. Noticeably, 3-fluorobenzyl benzimidazole derivative **5c** gave remarkable antimicrobial activities against *S. cerevisiae*, MRSA and *B. proteus* with MIC values of 1, 2 and 4 μg/mL, respectively. Experimental research revealed that compound **5c** could effectively intercalate into calf thymus DNA to form compound **5c**–DNA complex which might block DNA replication and thus exert antimicrobial activities. Molecular docking indicated that compound **5c** should bind with DNA topoisomerase IA through three hydrogen bonds by the use of fluorine atom and oxygen atoms in 5-fluorouracil with the residue Lys 423.

Pyrimidine ring is a six-membered aromatic heterocycle [1] bearing two nitrogen atoms, which extensively exists in biologically active natural products. The special heterocycle can readily interact with biological macromolecules like enzymes, receptors, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Thus, pyrimidine fragment has been prevalently employed in the design of new drugs and a lot of pyrimidines as drugs have been successfully developed and extensively used in clinic. Especially in antimicrobial aspects, many pyrimidine compounds such as sulfadiazine and voriconazole have been in widespread clinical use to treat diseases caused by bacteria and fungi. However, the increasing incidence of multidrug-resistant strains, intractable pathogenic microorganisms and newly emerging pathogens gradually limited their clinical application.[1] The development of new pyrimidine compounds have been an active topic in discovering highly potential antimicrobial agents. 5-Fluorouracil (5-FU), a known anticancer drug which target the nucleotide synthetic enzyme thymidylate synthase and disrupt DNA synthesis and thus inhibit the growth of cell,[2] is an antimetabolite of the pyrimidine derivative in which the fluoro and oxo groups play positive roles in exerting bioactivity. However, so far the 5-fluorouracil-based antimicrobial research has been seldom observed. Therefore, it is of great interest for us to employ pyrimidine-containing 5-FU as a constructing block to develop a series of hybrids of 5-FU and benzimidazole nucleus, and investigate their antimicrobial potency.

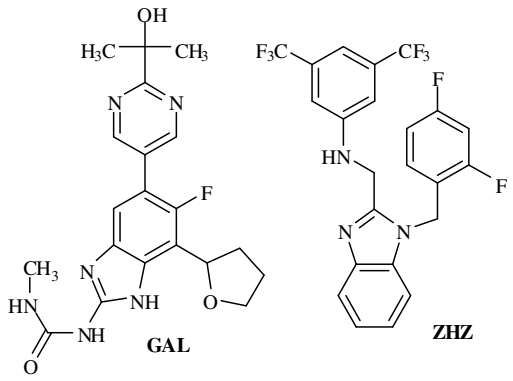

Figure 1. Structure of some antimicrobial benzimidazole derivatives.

Benzimidazoles exert various pharmacological activities such as antiparasitic, anticancer, antihistaminic, antihypertensive, antiulcer properties, and some of them have been successfully developed as clinical drugs.[3] This has drawn more and more concern to investigate the other medicinal application of benzimidazoles. Recently, extensive biochemical and pharmacological studies revealed that benzimidazoles possessed large potentiality to inhibit the growth of bacterial and fungal strains.[4] Benzimidazole is structurally similar to purine, and its derivatives could compete with purines, distinctly inhibiting the synthesis of nucleic acids and proteins, thereby killing bacterial strains or inhibiting their growth.[5] Several benzimidazoles have

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