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Mini-review

Bioactive thiazole and benzothiazole derivatives

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ABSTRACT

The heterocycles are the versatile compounds existing in almost all natural products and synthetic organic compounds, usually associated with one or the other biological activity. Among the heterocycles the thiazoles and benzothiazoles occupy a prominent position. They possess a broad range of biological activities and are found in many potent biologically active molecules and drugs such as vitamin thiamine, sulfathiazol (antimicrobial drug), ritonavir (antiretroviral drug), abafungin (antifungal drug) and tiazofurin (antineoplastic drug). The thiazole moiety is abundantly found in natural products while benzothiazole moiety is rare. In this review we disclose the literature reports of thiazoles and benzothiazoles possessing different biological activities.

1. Introduction

The thiazoles and benzathiazoles are found in a wide variety of bioactive molecules and natural products [1]. The terrestrial and marine organisms / microorganisms have been a prominent source of these heterocycles. These naturally occurring secondary metabolites or polyketides are often bioactive and a large bulk of literature is being published related to their isolation, chemistry and biology.

Thiazole and its derivatives have been of great scientific exploitation and interest as these are accompanied with almost all the biological and pharmacological activities, like antibacterial, antiprotozoal, antimalarial, anticancer [2], treat allergies [3], gene-modulating activities, antischizophrenia, antihypertension [4], anti-inflammation [5], anti-HIV infections [6] and many more.

The complex natural product antibiotics containing nitrogen heterocycle thiazole are secondary metabolites produced by actinomycetes [7], Gram-positive mycelial sporulating bacteria, largely of the genus Streptomyces. Many among this thiopeptide antibiotic family possess similar biological profile, with almost no activity against Gram-negative bacteria, whereas very active against Gram positive bacteria by inhibiting protein synthesis and are in many cases effective against methicillin-resistant *Staphylococcus aureus* (including multidrug-resistant *S aureus* strains (MRSA)) [8]. Their mode of action is based on inhibition of bacterial protein translation by blocking the ribosomal GTPase-associated center [1,3] or by inhibiting the translation factor EF-Tu.

2. Thiazoles and benzathiozoles as anticancer agents

Bleomycins (BLMs) and their related analogues are a family of glycopeptide antitumor antibiotics produced and isolated from the bacterium *Streptomyces* sp [9]. Glycopeptide antibiotics are a class of drugs, composed of glycosylated cyclic or polycyclic non-ribosomal peptides. These bleomycins (BLMs) have been clinically used to treat several types of cancers, like squamous cell carcinomas, malignant lymphomas and testicular cancers [10]. The bleomycin antibiotics act by the degradation of DNA [11] and RNA [12] in the presence of a metal ion and oxygen. Other derivatives like bleomycin A_5 (**1**) and bleomycin A_6 (**3**) have four domains and the C-terminal domain plays an important role in DNA binding. The analogue NC1101 (**2**) [9], isolated from *Streptomyces verticillus* var. *pingyangensis* n. var. contains a novel tetrahydropyrimidine ring in the terminal amine unit. This analogue shows higher growth-inhibitory activity against human tumor cells than BLM. Many other derivatives like peplomycin (**4**) were prepared and used in biological study. The methylvalerate domain of BLM plays an important role in DNA cleavage. The effect of the valerate moiety in the deglycoBLM A_6 (**5**) analogue has been studied using supercoiled DNA relaxation and sequence-selective DNA cleavage assays [13].

Tallysomycin (**6**) [14], a third generation bleomycin analogue, is an antitumor antibiotic that is structurally related to bleomycin and has been found to be more potent than bleomycin in the Walker 256 carcinoma and the P-388 leukemia tumor systems, as well as in

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a variety of bacteria and fungi. The mechanism of action of tallysomycin is similar to that of bleomycin and produces strand breaks in purified isolated DNA and intracellular DNA. Other derivatives of bleomycin, like Zorbamycin (**7**, ZBM) [15] isolated from *Streptomyces flaWoWiridis* ATCC 21892, and phleomycins (**8**, PLMs) [16] isolated from *S. verticillus*, binds to DNA and stimulate DNA breakage *in vitro* (Fig. 1).

Ascidians (tunicates) are the rich sources of the structurally diverse and pharmaceutically potent secondary metabolites. The cyclic peptides containing thiazole moieties like calyxamides A (**9**) and B (**10**), have been first isolated from the marine sponge *Discodermia calyx* collected near Shikine-jima Island, Japan. Later these were optimized for biological studies and it was observed that calyxamides A and B showed moderate cytotoxicity against P388 murine leukemia cells (Fig. 2) [17].

Leinamycin (**11**), a secondary metabolite isolated from *Streptomyces*, have been reported to possess antitumor activity [18]. Structurally the antibiotic is composed of a 18-membered

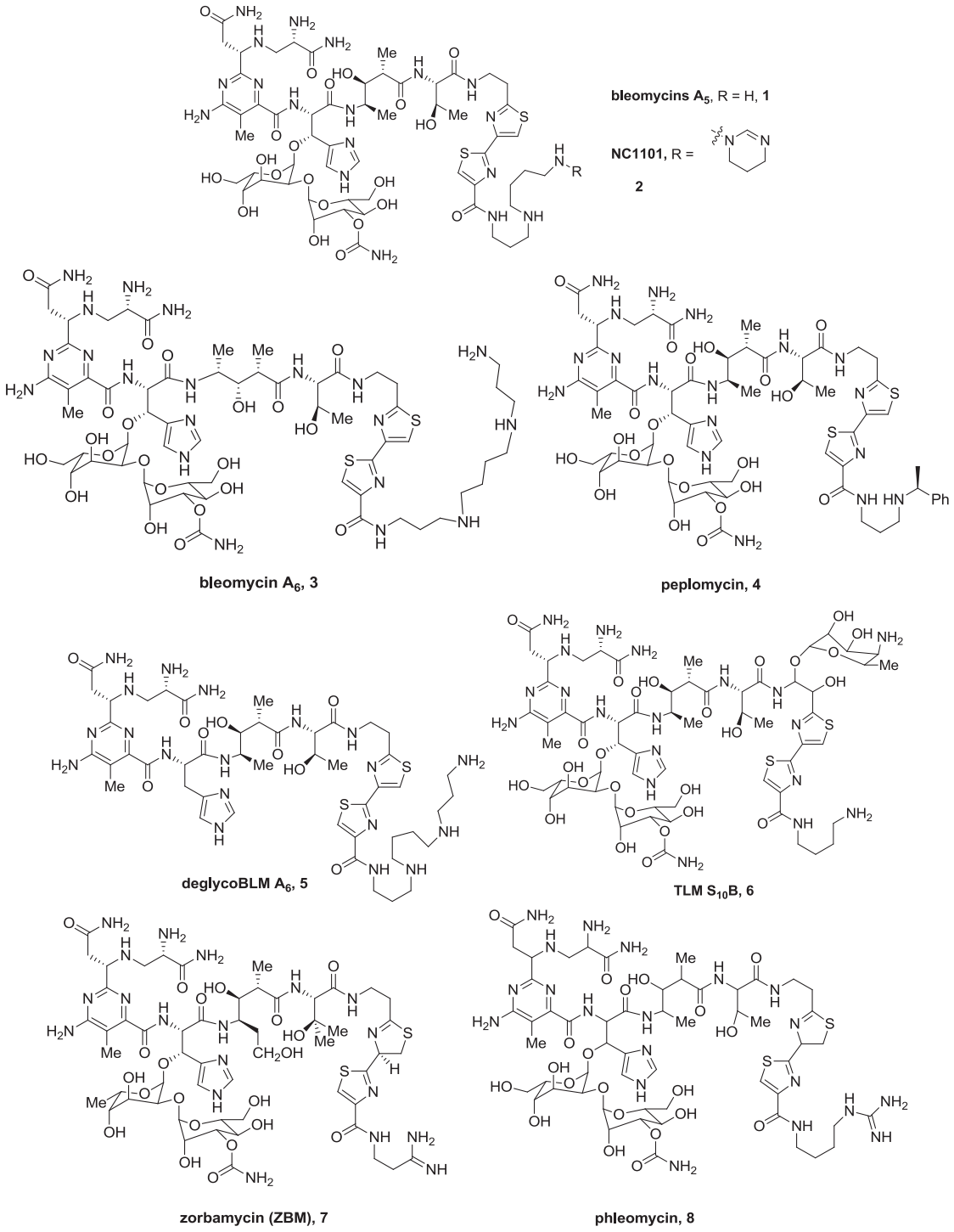

Fig. 1. Bleomycins (BLMs) and their related analogues.