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Bifunctional ethyl 2-amino-4-methylthiazole-5-carboxylate derivatives: Synthesis and *in vitro* biological evaluation as antimicrobial and anticancer agents

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ABSTRACT

Thirty thiazole compounds bearing chemotherapeutically-active pharmacophores were synthesized and evaluated for their preliminary *in vitro* antimicrobial and anticancer activities. Nineteen compounds displayed obvious antibacterial potential, with special bactericidal activity against Gram positive bacteria, whereas, nine analogs showed moderate to weak antifungal activity against *Candida albicans*. The analog **12f** proved to be the most active antimicrobial member identified in this study being comparable to ampicillin and gentamicin sulfate against *Staphylococcus aureus* and *Bacillus subtilis*, together with a moderate antifungal activity. Additionally, nine derivatives were tested for their preliminary *in vitro* anticancer activity according to the current one-dose protocol of the NCI. Compound **9b** revealed a broad spectrum of anticancer activity against 29 out of the tested 60 subpanel tumor cell lines. Collectively, compounds **4**, **9b**, **10b** and **12f** could be considered as promising dual anticancer antibiotics.

1. Introduction

Human struggle against life-threatening infectious diseases brought about by multi-drug resistant (MDR) Gram-positive and Gram-negative pathogenic bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE), is becoming a serious global dilemma [1]. In addition, the frequent occurrence of primary and opportunistic mycotic infections (particularly *Candida albicans*) is well documented especially among immuno-compromised patients experiencing AIDS, cancer and organ transplantation [2]. Consequently, such types of infections have spurred interest in the discovery of novel non-traditional antimicrobial agents that would not induce cross-resistance with classical antibiotics. On the other hand, the high mortality rates engaged with the rising number of diverse types of cancers, have triggered an unrivaled level of research aiming at finding out new unconventional lead structures that might be beneficial in designing novel antitumor agents [3]. It is self-evident that patients with neoplastic disorders who are subjected to chemotherapeutic treatment are mostly susceptible to microbial infections due to the subsequent drop of immunity. Therefore, co-administration of multiple drugs for treating patients suffering from cancer disease accompanied with microbial infections might inflict some added health problems especially in patients with impaired liver and/or kidney functions. Therefore, the concept of monotherapy by a single drug which would possess dual utility might be advantageous from both therapeutic and cost-effective stand points.

Over the past few years, the conspicuous role of thiazole derivatives in the field of chemotherapy is unmistakable, owing to their reported distinctive antimicrobial [4–7], antifungal [8,9], antitubercular [10,11] activities. Moreover, several thiazole-containing compounds were documented to contribute to a variety of antineoplastic potentials being employed as anticancer [12–14], cytotoxic [15,16], antiproliferative [17,18], DNA-cleaving [19], anti-angiogenic [20] and tubulin polymerization inhibiting [21] agents. Recently, it has been reported that some thiazoles were stemmed as novel inhibitors of metastatic cancer cell migration and invasion [22]. Interest in the chemotherapeutic activity of thiazoles was augmented by the discovery of the natural antineoplastic antibiotic tiazofurin (**A**; Fig. 1) [23], the documented DNA minor

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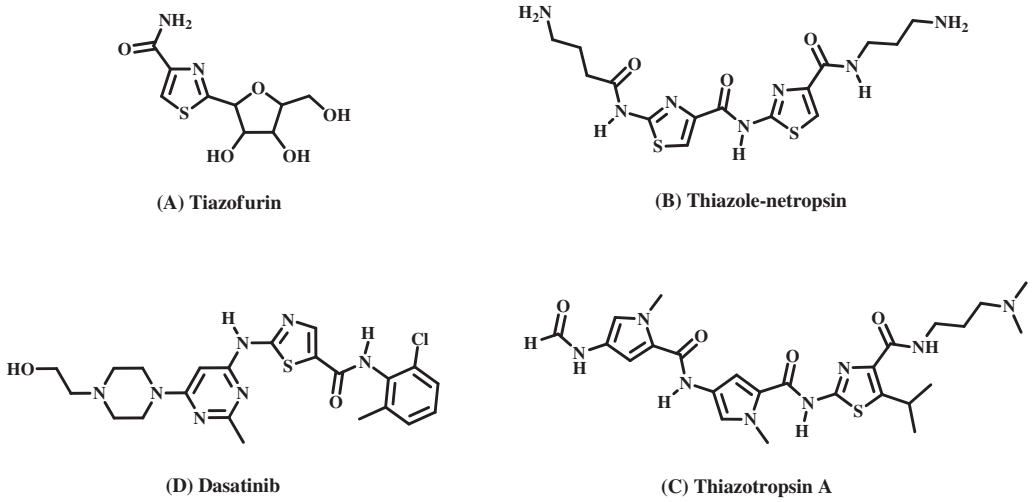

Fig. 1. Structures of tiazofurin (**A**), thiazole–netropsin (**B**), thiazotropsin A (**C**) and dasatinib (**D**).

groove binding property of thiazole–netropsin and thiazotropsin A (**B** and **C**; Fig. 1) [24,25], and the evidenced clinical antitumor effectiveness of bleomycin and leinamycin [26]. Furthermore, another thiazole derivative; dasatinib (**D**; Fig. 1) was reported to possess potential tyrosine kinase inhibitory activity, and proved to be efficient in the treatment of imatinib-resistant mutants [27]. Most of the previously-described compounds are distinguished by encountering, as a prevalent character, a substituted carboxamido functional group(s) linked to a thiazole ring.

In view of the above mentioned facts, and inspired by the promising antimicrobial and anticancer activities associated with some thiazole-containing compounds reported in our previous publications [28–38], we report herein the synthesis, *in vitro* antimicrobial and anticancer evaluation of some novel bifunctional ethyl 2-amino-4-methylthiazole-5-carboxylate derivatives. The thrust of efforts in structure modification of such type of compounds focussed mainly on derivatization of the amino group at position-2 of the thiazole ring into the chemotherapeutically-active azomethine, *N*-formyl, *N*-acyl, sulfonamido, ureido and thioureido functionalities. In addition, the conversion of the ester function at position-5 to the carboxamido and acid hydrazide groups was taken into consideration based on the reported facts about their effective contribution in many potential chemotherapeutic activities [39,40]. The variability in the nature of substituents at such functionalities was attempted to represent different electronic, lipophilic and steric environment that would influence the targeted biological activities. Agar-diffusion method was used for the evaluation of the antimicrobial activity, and the minimal inhibitory (MIC, μg/mL) and minimal bactericidal (MBC, μg/mL) concentrations for the active compounds were determined [41–43]. On the other hand, the anticancer activity was evaluated according to the current protocol of the National Cancer Institute (NCI) *in vitro* disease-oriented human cells screening panel assay [44–46].

2. Results and discussion

2.1. Chemistry

Synthesis of the intermediate and target compounds **2**–**13** was performed according to the reactions illustrated in Schemes 1 and 2. The key intermediate in this study is ethyl 2-amino-4-methylthiazole-5-carboxylate **1** [47]. Condensing **1** with the appropriate heterocyclic aldehyde in acetic acid medium afforded the corresponding azomethines **2a**–**c** in good yields. Heating of the starting compound **1** with formic acid furnished the *N*-formyl derivative **3**. Its IR spectrum revealed an additional carbonyl band at 1650 cm^{-1} attributed to the new aldehyde (C=O) function, whereas the ^1H NMR spectrum (δ-ppm) exhibited a new singlet at δ 8.63 ppm due to the aldehydic proton. Furthermore, acylation of the thiazole **1** with 3,4,5-trimethoxybenzoyl chloride gave rise to the expected ethyl *N*-(3,4,5-trimethoxybenzoyl)-2-amino-4-methylthiazole-5-carboxylate **4**. Analogously, reacting **1** with benzenesulfonyl chloride or p-toluenesulfonyl chloride led to the introduction of a substituted phenylsulfonyl moiety at position-2 with the formation of the *N*-(5-ethoxycarbonyl-4-methylthiazol-2-yl)-4-substituted benzenesulfonamides **5a**,**b**. Their IR spectra showed additional bands at 1017–1110 cm^{-1} attributed to the (SO_2) function. Moreover, the 2-trifluoroacetylamino derivative **6** was successfully prepared by warming the start **1** with trifluoroacetic anhydride. On the other hand, the 2-amino function of the start **1** was alkylated with chloroacetyl chloride in dry toluene to produce the intermediate **7**. The chlorine atom of the latter was displaced by either morpholine or *N*-methyl piperazine to produce the target compounds **8a**,**b** (Scheme 1).

At this stage, some 1-(5-ethoxycarbonyl-4-methylthiazol-2-yl)-3-substituted ureas **9a**,**b** were successfully prepared by condensing the key intermediate thiazole **1** with the appropriate isocyanates in pyridine as alkaline medium. Their IR spectra showed new bands at 1645–1650 cm^{-1} corresponding to the ureido carbonyl group. In their turn, when **9a**,**b** were reacted with hydrazine hydrate, the corresponding targeted 4-methyl-2-(*N*-substituted ureido)-thiazole-5-carboxylic acid hydrazides **10a**,**b** were obtained. In an analogous fashion, when the thiazole **1** was condensed with the appropriate isothiocyanates in pyridine, the corresponding thioureas **11a**–**f** were achieved. The IR spectra of these thioureido derivatives revealed the characteristic C=S band at 982–958 cm^{-1} beside the absorption bands of the ester C=O group at 1730–1718 cm^{-1}. Similarly, the targeted 4-methyl-2-(*N*-substituted thioureido)-thiazole-5-carboxylic acid hydrazides **12a**–**f** were obtained by heating **11a**–**f** with hydrazine hydrate. The ^1H NMR spectra (δ-ppm) of the acid hydrazides **10a**,**b** and **12a**,**b** were characterized by the disappearance of the triplets and quartets of the ethyl ester and the appearance of new singlets attributed to the amides NH proton at their respective chemical shifts. Finally, refluxing the thiazole ester **1** with the appropriate amine in ethanol resulted in the formation of the corresponding