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Original article

Synthesis and anticancer activity evaluation of 4-thiazolidinones containing benzothiazole moiety

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ABSTRACT

Antitumor screening of several novel 4-thiazolidinones with benzothiazole moiety has been performed. Reactions of (benzothiazole-2-yl)hydrazine with trithiocarbonyl diglycolic acid or 6-methyl-2-amino-benzothiazole with 2-carbethoxymethylthio-2-thiazoline-4-one have yielded starting 3- (**1**) or 2-substituted (**11**) 4-thiazolidinones which have been subsequently utilized in a Knoevenagel condensation for obtaining a series of 5-arylidene derivatives **2**–**10**, **12**–**16**. Compound **11** has been obtained alternatively by a counter synthesis method based on the reaction of 2-chloro-N-(6-methylbenzothiazol-2-yl)-acetamide and ammonium thiocyanate. The structures of compounds have been determined by ^{1}H, ^{13}C NMR, IR and X-ray analysis. *In vitro* anticancer activity of the synthesized compounds was tested by the National Cancer Institute and two (**6**, **16**) of them has revealed the anticancer activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers cell lines. Among tested compounds, 2-{2-[3-(benzothiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidenemethyl]-4-chlorophenoxy}-N-(4-methoxyphenyl)-acetamide (**6**) was found to be the most active candidate with average $logGI_{50}$ and logTGI values −5.38 and −4.45 respectively.

1. Introduction

4-Thiazolidinone ring system is a core structure in various synthetic compounds displaying broad spectrum of biological activities [1], including an anticancer effect [2–5]. Mechanisms of 4-thiazolidinones and related heterocycles antitumor activity may be associated with the affinity to anticancer biotargets, such as phosphatase of a regenerating liver (PRL-3) [6,7], nonmembrane protein tyrosine phosphatase (SHP-2) [8], JNK-stimulating phosphatase-1 (JSP-1) [9], tumor necrosis factor TNFα [10], anti-apoptotic biocomplex Bcl-X_L-BH3 [11], integrin $\alpha_v\beta_3$ [12], etc. Necroptosis inhibitors have been recently identified among 4-thiazolidinones [13]. On the other hand benzothiazole ring belongs to the privilleged scaffolds in modern medicinal chemistry [14] particularly in discovering of new anticancer agents. Various benzothiazole derivatives were proposed as inhibitors of fatty acid amide hydrolase (FAAH) [15], Raf kinase (Raf-1) [16] and B-cell lymphoma protein BCL-2 [17]. 5-Arylidene derivatives were previously shown as the most active group of compounds with the anticancer activity among large pull of 4-azolidone derivatives and analogs [18]. During the studies presented in this article we have found that attachment of benzothiazole moiety to 5-arylidene-thiazolidinone scaffold allowed as gaining of 1 log of activity (at GI_{50} level) in comparison to 2/3-unsubstituted analogous compound samples. Consequently, the combination of 4-thiazolidinone template with benzothiazole moiety in one molecule can be considered as promising approach in drug-like molecules design (Fig. 1) which has already been partially confirmed by the discovery of MKT 077 [19] reported as a registered antitumor agent. In this spirit, herein we describe the synthesis and anticancer activity of new 4-thiazolidinones with benzothiazole moiety.

2. Results and discussion

2.1. Chemistry

The general synthetic pathways of targeted benzothiazole substituted 4-thiazolidinones are depicted in Schemes 1 and 3

We synthesized 3-(benzothiazol-2-ylamino)-2-thioxo-4-thiazolidone (**1**) from (benzothiazole-2-yl)hydrazine and trithiocarbonyl

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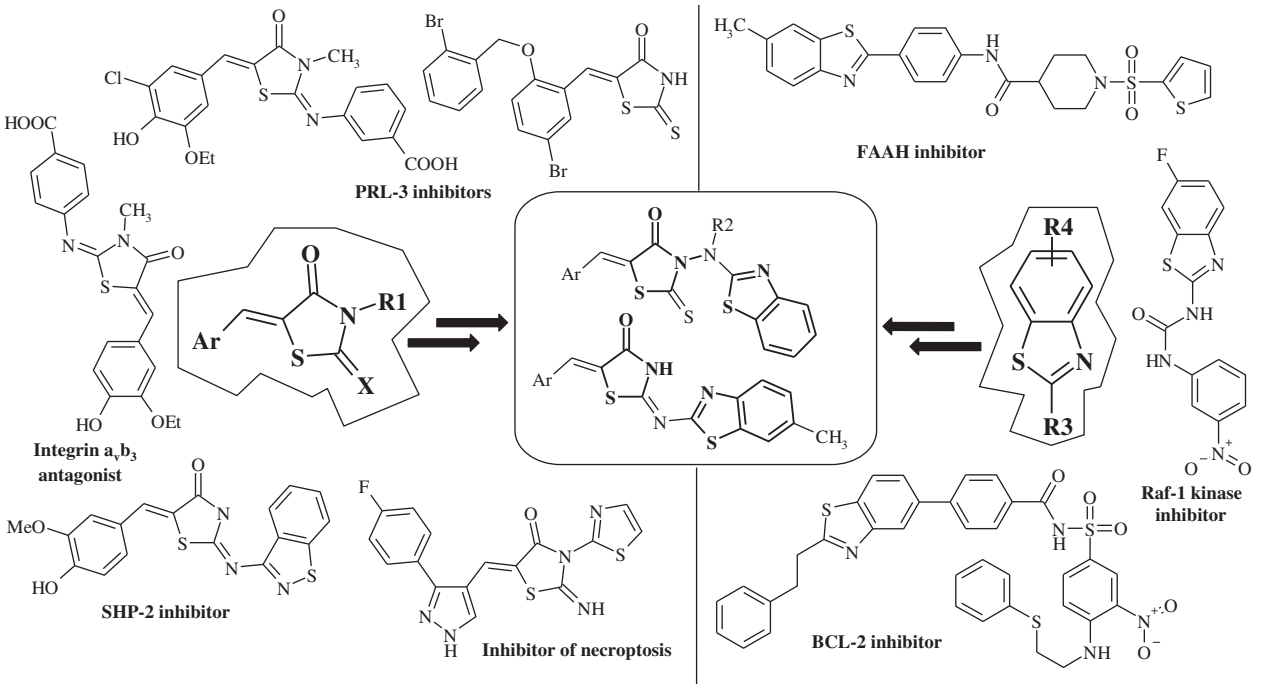
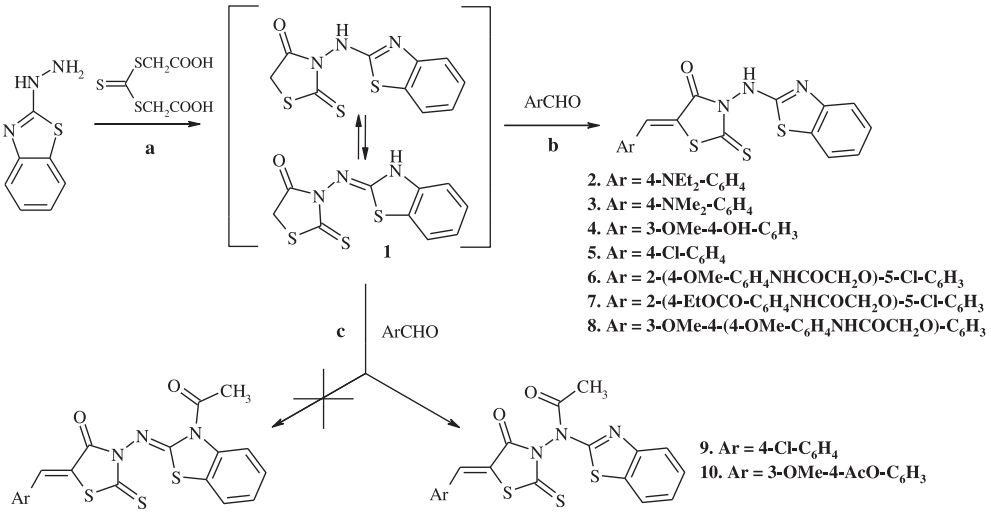


Fig. 1. Structures of anticancer 4-thiazolidinones and benzothiazoles and background for target compounds synthesis.

diglycolic acid [20] in refluxing ethanol with the yield of 78%. The synthesized methylene active derivative **1** was readily reacted with aromatic aldehydes to produce 5-arylidene derivatives **2**–**8**, using a Knoevenagel condensation procedure (medium – acetic acid, catalyst – fused sodium acetate) [1,3,21]. The acetylation of exocyclic nitrogen was observed (**9**–**10**) following acetic anhydride addition to reactive mixture. This fact clearly proved that compound **1** had reacted in hydrazine tautomeric form (Scheme 1), although the characteristic feature of the mentioned substance and its 5-arylidene derivatives **2**–**8** is hydrazone-hydrazine tautomerism (Scheme 2). Additionally, both tautomer forms may exist as a mixture of two stereoisomers (A,C and B,D), which are particularly stabilized by the formation of intramolecular hydrogen bonds.

The prototropic tautomerism and stereoisomerism among this class of compounds was confirmed by spectral data, both in solution and in the solid state. Spectroscopic studies revealed characteristic multiplication of signals in IR, ^{1}H and ^{13}C NMR spectra, observed for some compounds and connected with the co-existence of different tautomeric forms. Thus, in ^{1}H NMR spectra of compounds **1**–**8** NH proton appears as two singlets at ~11.60 ppm and ~12.45 ppm and benzothiazole moiety forms subspectrum of multiplets at ~7.05–7.55 ppm. A *Z*-configuration of the exocyclic C=C bond in the 5-arylidene derivatives **2**–**10** was confirmed by the signal of a methine proton, which resonated at higher chemical shift (~7.80 ppm) as a broad singlet [22,25]. In the solid state, the existence of compounds **1**–**8** in tautomeric



Scheme 1. Synthesis of 3-(benzothiazol-2-ylamino)-2-thioxo-4-thiazolidinones. Reagents, conditions and yields: (a) EtOH, reflux 5h, 78%; (b) AcONa, AcOH, reflux 2h, 59–78%; (c) AcONa, AcOH, Ac_2O, reflux 2h, 71–74%.