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Original article

Synthesis of novel thiazolone-based compounds containing pyrazoline moiety and evaluation of their anticancer activity

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ABSTRACT

To examine the anticancer activity several novel thiazolone-based compounds containing 5-aryl-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl framework were obtained. Reaction of 5-aryl-3-phenyl-4,5-dihydropyrazole with 4-thioxo-2-thiazolidinone or 2-carbethoxymethylthio-2-thiazoline-4-one yielded starting 4- (**1** and **2**) or 2-substituted (**11** and **12**) thiazolones which were utilized in Knoevenagel condensation for obtaining a series of 5-arylidene derivatives **3**–**10**, **13**–**18**. Alternatively **11**, **12** and their 5-arylidene derivatives were synthesized by means of 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazoline as S,N-binucleophile via [2 + 3]-cyclocondensation approach. The structures of compounds were determined by ^{1}H, ^{13}C NMR, LC–MS, EI-MS and X-ray analysis. The *in vitro* anticancer activity of synthesized compounds were tested by the National Cancer Institute and most of them displayed anticancer activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancer cell lines. Relations between structure and activity are discussed, the most efficient anticancer compound **16** was found to be active with selective influence on colon cancer cell lines, especially on HT 29 ($\log GI_{50} = -6.37$).

1. Introduction

Thiazolidine template is one of the privileged structure fragments in modern medicinal chemistry considering its broad pharmacological spectrum and affinity for various biotargets of these class heterocyclic compounds [1]. Some of thiazolidine derivatives, especially 4-thiazolidinones, are PPAR-receptors agonists showing hypoglycemic, antineoplastic and anti-inflammatory activities [2], complex COX-2/5-LOX inhibitors [3] or phospholipase A_2 (PLA_2) [4] possessing anti-inflammatory action, and UDP-MurNAc/L-Ala-ligase inhibitors with antimicrobial effect [5]. Antineoplastic properties of 4-thiazolidinones and related heterocycles can most probably be caused by their affinity to anticancer biotargets, such as JNK-stimulating phosphatase-1 (JSP-1) [6], tumor necrosis factor TNFα [7], anti-apoptotic biocomplex Bcl-X_L-BH3 [8], integrin $\alpha_v\beta_3$ receptor [9], etc. It must be emphasized, that combination of thiazolidine template with other heterocycles is a well-known approach for drug-like molecules' build-up, which allows to achieve new pharmacological profile, action strengthening or toxicity lowering [1]. As part of our ongoing research in discovery of new active anticancer compounds [10–12] in this work we try to study the influence of pyrazoline moiety and thiazolone scaffold combination on the anticancer effect. The structural variations were explored by placing the pyrazoline moiety in positions 2 or 4 and introduction of different arylidene substituents in position 5 of thiazolone moiety (Fig. 1). The latter were recently exploited as bioactive arms on heterocyclic scaffolds useful to pharmacological effect realization of thiazolidinone based compounds.

2. Results and discussion

2.1. Chemistry

The general methods for synthesis of target pyrazoline substituted thiazolones are depicted in Schemes 1 and 2.

4-(5-Aryl-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1,3-thiazol-2(5*H*)-ones **1** and **2** were obtained by means of 4-thioxo-2-thiazolidinone (isorhodanine) reaction with appropriate 5-aryl-3-phenyl-2-pyrazoline in refluxing ethanol (Scheme 1). Aiming at the detailed elaboration of structure–activity relationship isomeric 2-(5-aryl-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1,3-thiazol-4(5*H*)-ones **11** and **12** were synthesized (Scheme 2). It should be noted, that 2-thioxo-4-thiazolidinone (rhodanine) usage for synthesis of target compounds failed. Therefore with the aim of increasing the

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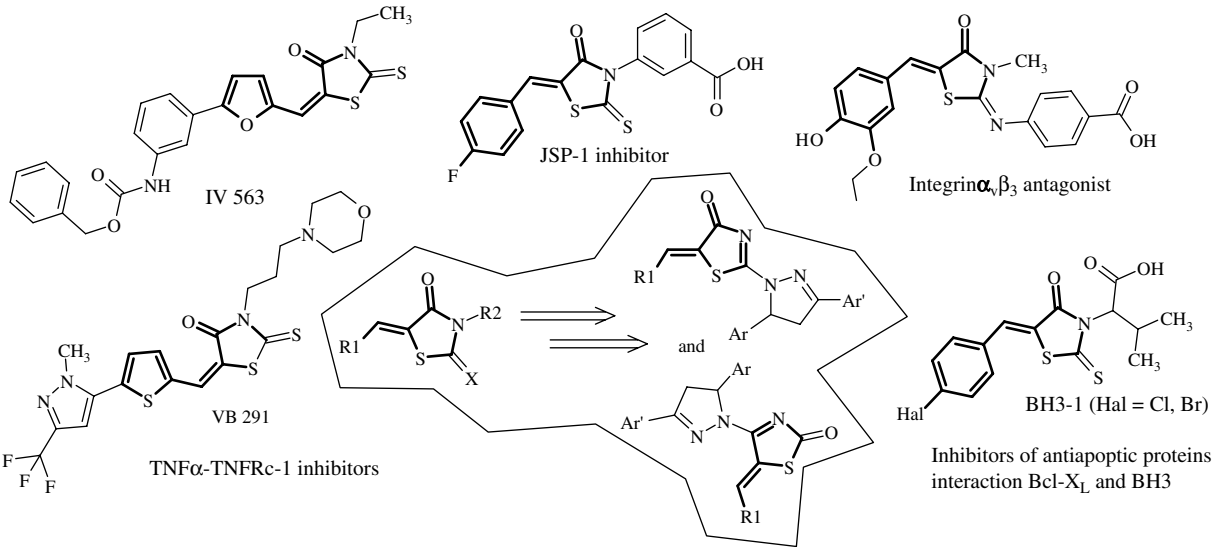


Fig. 1. Structures of anticancer 4-thiazolidinones and rationale for thiazolone-based compounds with pyrazoline moiety synthesis.

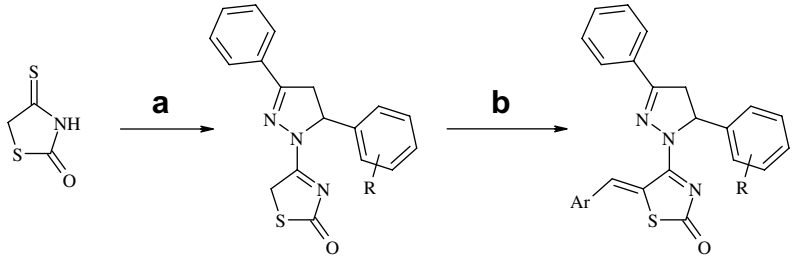
rhodanine reactivity, the latter was alkylated via intermediate triethylammonium salt by ethylchloroacetate in refluxing acetone, as reported [13]. Following reaction of 2-carbethoxymethylthio-2-thiazoline-4-one with appropriate 5-aryl-3-phenyl-2-pyrazolines in refluxing ethanol target 2-(5-aryl-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1,3-thiazol-4(5*H*)-ones were obtained. Alternatively compounds **11** and **12** were synthesized following [2 + 3]-cyclo-condensation of 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines with chloroacetic acid in the presence of fused sodium acetate in refluxing acetic acid.

Synthesized compounds **1**, **2** and **11**, **12** are methylene active heterocycles. On the other hand, it was previously established [1,13], that in most cases the presence and nature of moiety in position 5 of thiazolidinones play the key role in realization and character of pharmacological effects. The above mentioned thesis was rationale for synthesis of new 5-arylidene derivatives **3**–**10**, **13**–**18**, using standard Knoevenagel reaction procedure (medium – acetic acid, catalyst – fused sodium acetate) [1,13]. Some compounds (**11**, **12**, **14**, **17** and **18**) were prepared alternatively by one-pot methodology involving reaction of 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines with chloroacetic acid and appropriate aromatic aldehydes in the presence of fused sodium acetate in refluxing acetic acid (Scheme 2).

The characterization data of synthesized novel pyrazoline substituted thiazolones are presented in experimental part. Analytical and spectral data (^{1}H NMR, ^{13}C NMR, LC–MS, EI-MS) confirmed the structure of the synthesized compounds.

Protons CH_2–CH of pyrazoline fragment in the ^{1}H NMR spectra of synthesized compounds show characteristic patterns of an AMX system. The chemical shifts of the protons H_A, H_M, and H_X have been assigned to about $\delta \sim 3.26$–3.45, $\delta \sim 3.96$–4.17, and $\delta \sim 5.68$–6.13, respectively, with corresponding coupling constants of $J_{AM} = 17.9$–18.6, $J_{Ax} = 10.4$–11.6, and $J_{Mx} = 2.9$–4.5 Hz. The chemical shift for the methylidene group of 5-arylidene derivatives **3**–**10** and **13**–**18** is insignificantly displaced in weak magnetic field, $\delta \sim 9.0$ and $\delta \sim 7.5$, respectively, and clearly indicated that only *Z*-isomers were obtained in Knoevenagel reaction of pyrazoline substituted thiazolones with aromatic aldehydes [15].

Structural features of synthesized 4-(5-aryl-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1,3-thiazol-2(5*H*)-ones were confirmed by X-ray crystallographic analysis of exemplified compound **5**. As follows from the X-ray analysis the compound obtained has the structure of



1. R = 2-OH
2. R = 4-OMe

3. R = 2-OH, Ar = Ph
4. R = 2-OH, Ar = 4-Cl-C_6H_4
5. R = 2-OH, Ar = 4-Br-C_6H_4
6. R = 2-OH, Ar = 4-OH-C_6H_4
7. R = 2-OH, Ar = 4-OMe-C_6H_4
8. R = 4-OMe, Ar = 4-Cl-C_6H_4
9. R = 4-OMe, Ar = 4-NMe_2-C_6H_4
10. R = 4-OMe, Ar = 4-NO_2-C_6H_4

Scheme 1. Synthesis of novel 4-(5-aryl-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1,3-thiazol-2(5*H*)-ones. Reagents, conditions and yields: (a) 5-(2-hydroxy or 4-methoxyphenyl)-3-phenyl-2-pyrazoline (1.0 equiv), EtOH, reflux 1 h, 62–67%; (b) Ar-CHO (1.1 equiv), AcONa (1.0 equiv), AcOH, reflux 2 h, 52–72%.