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Novel 3-aroyl-5-arylidene-1,3-thiazolidine-2,4-diones: synthesis and antitumor activity

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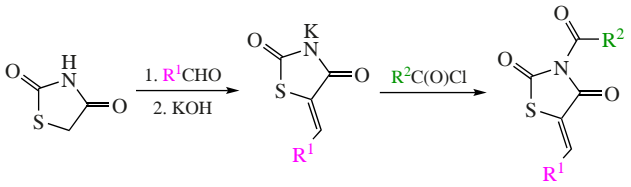
New 3-aroyl-5-arylidene-1,3-thiazolidine-2,4-diones were prepared by the Knoevenagel condensation of 1,3-thiazolidine-2,4-dione with aromatic aldehydes, conversion of the thus obtained 5-arylidene derivatives into the corresponding *N*-potassium salts, and their final *N*-acylation with acyl chlorides. The *in vitro* antitumor efficacy of the compounds was evaluated by the MTT method.



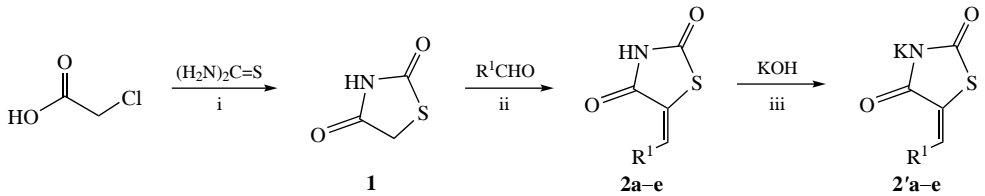
Keywords: 1,3-thiazolidine-2,4-diones, Knoevenagel condensation, *N*-acylation, MTT method, antiproliferative activity.

Cancer is currently the most serious disease threatening human life and health.[1] Targeted therapies represent a good way to treat key targets of cancer.[2] Small-molecule antitumor drugs are currently in a focus of research.[3–7] Among them, thiazolidine derivatives known for their diverse biological activities are particularly noteworthy, and 1,3-thiazolidine-2,4-diones have demonstrated the ability to inhibit tumor cell growth by engaging multiple targets and pathways. Some thiazolidinones inhibit the expression of the antiapoptotic protein BCL-2, a key factor in cancer cell survival.[8] B-cell lymphoma-2 (BCL-2) is essential for maintaining tissue homeostasis and preventing cancer development,[9,10] and action of this protein toward tumor cells has been multiply documented in recent years.[11–20]

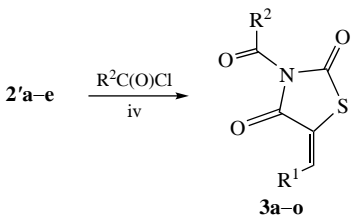
In the present work, we employed a rational approach utilizing molecular hybridization and the principle of bioisosterism in the design of novel 1,3-thiazolidine-2,4-dione derivatives. We selected four BCL-2 overexpressing human cancer cell lines, *viz*. SW620 (colon cancer), A549 (non-small cell lung cancer), HeLa (cervical cancer), and MCF-7 (breast cancer) for *in vitro* evaluation. Cisplatin, known for its broad-spectrum antitumor activity, was used as a positive control to assess the antiproliferative effects of our synthesized thiazolidinedione compounds.

The synthesis of the target compounds started from 1,3-thiazolidine-2,4-dione **1** readily available by heterocyclization between chloroacetic acid and thiourea (Scheme 1).[21–23] Subsequently, various aromatic aldehydes were reacted with CH-acid **1** *via* the Knoevenagel condensation to produce 5-arylidene intermediates **2a–e** (*cf.* ref. 24). Intermediates **2a–e** were then treated with potassium hydroxide to afford the corresponding amine salts **2′a–e** (*cf.* ref. 25) which were finally *N*-acylated with acyl chlorides to produce the desired compounds **3a–o** (*cf.* ref. 26)

The CH-acidity of compound **1** enabling its Knoevenagel condensation is apparently provided by two electron-withdrawing oxo groups. However, its NH group also exhibits weak acidic



2a, 2′a R^1 = 2-FC_6H_4 **2d, 2′d** R^1 = 4-MeC_6H_4
2b, 2′b R^1 = 2-ClC_6H_4 **2e, 2′e** R^1 = 2,3,4-$(MeO)_3C_6H_2$
2c, 2′c R^1 = 2-BrC_6H_4



3a R^1 = 2-FC_6H_4, R^2 = 2-thienyl
3b R^1 = 2-FC_6H_4, R^2 = 4-MeC_6H_4
3c R^1 = 2-FC_6H_4, R^2 = 2-$MeOC_6H_4$
3d R^1 = 2-ClC_6H_4, R^2 = 4-ClC_6H_4
3e R^1 = 2-ClC_6H_4, R^2 = 2-thienyl
3f R^1 = 2-ClC_6H_4, R^2 = 2-$MeOC_6H_4$
3g R^1 = 2-BrC_6H_4, R^2 = 4-ClC_6H_4
3h R^1 = 2-BrC_6H_4, R^2 = 2-thienyl
3i R^1 = 2-BrC_6H_4, R^2 = 4-MeC_6H_4
3j R^1 = 4-MeC_6H_4, R^2 = 4-ClC_6H_4
3k R^1 = 4-MeC_6H_4, R^2 = 2-thienyl
3l R^1 = R^2 = 4-MeC_6H_4
3m R^1 = 2,3,4-$(MeO)_3C_6H_2$, R^2 = 4-ClC_6H_4
3n R^1 = 2,3,4-$(MeO)_3C_6H_2$, R^2 = 4-MeC_6H_4
3o R^1 = 2,3,4-$(MeO)_3C_6H_2$, R^2 = 2-$MeOC_6H_4$

Scheme 1 *Reagents and conditions*: i, HCl, H_2O, reflux; ii, AcONa, AcOH, reflux; iii, KOH, EtOH, reflux; iv, acetone, room temperature.

Table 1 *In vitro* antiproliferative activity of novel 1,3-thiazolidine-2,4-diones against A549, HeLa, MCF-7 and SW620 tumor cell lines.

Compound	IC_{50}/μM			
	A549	HeLa	MCF-7	SW620
3a	39.3	>50	35.6	19.6
3b	35.5	>50	46.3	26.8
3c	>50	48	>50	>50
3d	>50	>50	>50	30.5
3e	>50	>50	46.5	>50
3f	>50	>50	>50	>50
3g	>50	48.3	>50	33.6
3h	>50	42.1	40.8	46.6
3i	31.8	29.1	>50	>50
3j	>50	>50	>50	>50
3k	29.6	48.6	>50	>50
3l	>50	42.1	>50	>50
3m	>50	>50	>50	>50
3n	>50	>50	>50	>50
3o	>50	>50	>50	>50
Cisplatin	6.1	5.4	13.9	10.8

character, which may prevent the Knoevenagel process under strongly basic conditions. To pursue the reaction, we selected anhydrous ethanol with AcONa/AcOH as the optimal catalyst/solvent system.[27] The conversion of thiazolidinediones **2** into their *N*-potassium salts **2′** can be performed in anhydrous ethanol either at room temperature or under reflux. However, the first method requires the use of much saturated potassium hydroxide in ethanol which is prone to deterioration and difficult to store, necessitating immediate use and resulting in cumbersome operations and solvent waste. In contrast, the second method not only provides a shorter reaction time and complete conversion but also minimizes reagent waste and reduces production costs, which is evidently preferential.

The antiproliferative activity of the obtained compounds **3a**–**o** was evaluated using the MTT assay (Table 1, see also Online Supplementary Materials, Figure S17). The results indicate that the structure of the R^1 substituent has a large influence on the *in vitro* antiproliferative activity. The activity analysis showed that compounds **3d**,**e**,**f** having the same R^1 possessed close activity against the four tumor cells while the R^2 structures were different. In contrast, the difference in R^1 nature of compounds **3a**,**e**,**h**,**k** was the cause for the differences in their antiproliferative activities. For instance, the activity of **3a** (IC_{50} = 19.6 μM) was significantly different from that of **3e** (IC_{50} > 50 μM), **3h** (IC_{50} = 46.6 μM) and **3k** (IC_{50} > 50 μM), and differences in SW620 activity also took place. For A549 and Hela, compounds with R^1 containing F and Br atoms and *p*-methyl groups had better antiproliferative activities, with **3k** (IC_{50} = 29.6 μM) having the best activity against A549 and **3i** (IC_{50} = 29.1 μM) having better activity against Hela. For MCF-7, fluorine-containing compounds in R^1 had better activity than those containing Cl and Br atoms, **3a** (IC_{50} = 35.6 μM) > **3h** (IC_{50} = = 40.8 μM) > **3e** (IC_{50} = 46.5 μM). Compared to the halogen group with an electron-withdrawing substituent on the benzene ring of R^1, methyl and methoxy electron-donating substituent did not have a significant inhibitory effect on SW620 cancer cells, and all of them had an IC_{50} value greater than 50 (not shown in Table 1 and Scheme 1). The halogen atoms in the electron-withdrawing group showed better inhibitory activity against SW620 cells, with **3a** (IC_{50} = 19.6 μM) > **3b** (IC_{50} = 26.8 μM) > **3d** (IC_{50} = 30.5 μM) > **3h** (IC_{50} = 46.6 μM), and the order of the halogen atoms in the substituent group could be analyzed as follows F > Cl > Br, the stronger the electron absorption ability, the stronger the activity.

To summarize, the R^1 (arylidene moiety) nature in novel 3-aroyl-5-arylidene-1,3-thiazolidine-2,4-diones **3** has a greater influence on their *in vitro* antiproliferative activity than that of R^2 (aroyl moiety). Given the relatively potent activity of these compounds, they can serve as promising leads for further structural modifications, aiming to enhance the antitumor potency of subsequent compound designs.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7605.

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