PHARMACIA

Pharmacia 70(4): 1093–1100
DOI 10.3897/pharmacia.70.e102449

Research Article

Synthesis and antitumor activity of 1,3,4-oxadiazole substituted 2-(5-ylidene-2,4-dioxothiazolidin-3-yl)-acetamides

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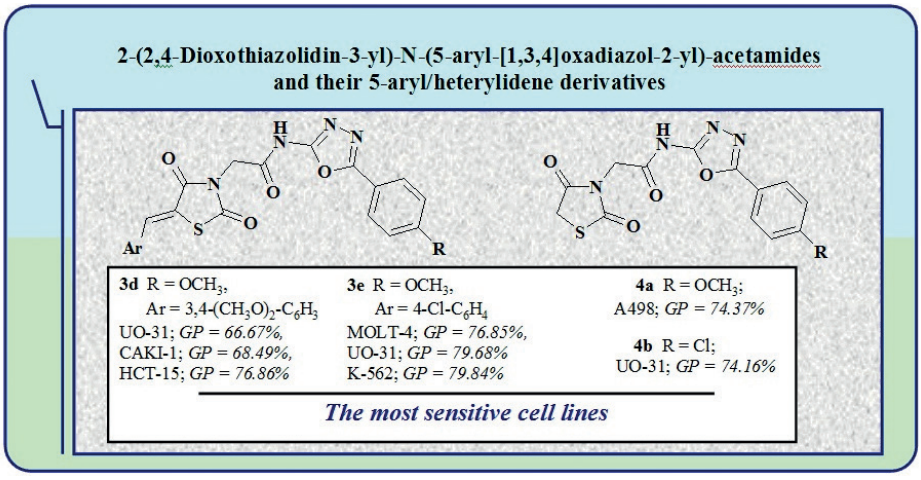
Received 21 February 2023 ♦ **Accepted** 27 June 2023 ♦ **Published** 12 October 2023

Citation: Lelyukh M, Kalytovska M, Zastryzhna M, Savchenko A, Chaban I, Harkov S (2023) Synthesis and antitumor activity of 1,3,4-oxadiazole substituted 2-(5-ylidene-2,4-dioxothiazolidin-3-yl)-acetamides. Pharmacia 70(4): 1093–1100. https://doi.org/10.3897/pharmacia.70.e102449

Abstract

A series of novel 1,3,4-oxadiazole substituted 2-(5-aryl/heterylidene-2,4-dioxothiazolidine-3-ylidene)-acetamides and their 5-unsubstituted analogues have been synthesized following *N*-alkylation reaction of 2-chloro-*N*-(5-aryl-[1,3,4]oxadiazol-2-yl)-acetamides with thiazolidinedione and potassium salts of its arylidene derivatives. The structures of target compounds were confirmed by using 1H NMR spectroscopy and elemental analysis. Evaluation of anticancer activity *in vitro* for the synthesized compounds was performed in accordance with the National Cancer Institute protocol. A selective influence of some tested compounds against leukaemia MOLT-4 (**3e**, GP = 76.85%) and K-562 (**3e**, GP = 79.84%), colon cancer HCT-15 (**3d,** GP = 76.86%), renal cancer A498 (**4a,** GP = 74.37%), CAKI-1 (**3d,** GP = 68.49%) and UO-31 (**3b-e, 4a-b**, GP = 66.67 ÷ 86.30%) cell lines was established.

Grafical abstract:



Keywords

organic synthesis, 4-thiazolidinones, 1,3,4-oxadiazoles, anticancer activity

Introduction

4-Thiazolidinone is the privileged scaffold in the modern medicinal chemistry which possesses the essential synthetic and therapeutic potential and applied as important construction motif for the development of novel highly active molecules (Jain et al. 2013; Tripathi et al. 2014; Agrawal 2021). Among the significant diversity of pharmacological properties the antitumor profile for 4-thiazolidinone derivatives is one of the most established and fundamental (Revelant et al. 2015; Singh et al. 2019; Tahmasvand et al. 2020; Subtelna et al. 2021). Mechanisms of 4-thiazolidinone antitumor action is associated with the affinity to cancer biotargets, such as tyrosine phosphatase (Geronikaki et al. 2008), cyclin dependent kinase CDK2 (Richardson et al. 2007), phosphatase of a regenerating liver PRL-3 (Park et al. 2008), JNK-stimulating phosphatase-1 JSP-1 (Cutshall et al. 2005), anti-apoptotic Bcl-2 proteins (Fu et al. 2015) etc. Furthermore, thymidylate synthase (Alzhrani et al. 2020), T315I-mutated Bcr-Abl kinase (Muhammad et al. 2017) and tubulin polymerization (Sigalapalli et al. 2021) inhibirors have been recently identified among 4-thiazolidinone derivatives. It's well known, that modification of the C5 position of 4-thiazolidinone core by introduction of 5-arylidene fragment is one of the most prominent approach to enhance and expand the pharmacological profile for this class of compounds. Thus, the essential influence of the presence/nature of C5 substituent on the pharmacological effects of 5-arylidene-4-thiazolidinones including anticancer action was confirmed and reported in different scientific papers (Maccari et al. 2011; Romagnoli et al. 2013; Chawla et al. 2019; Türe et al. 2021; Lelyukh et al. 2023).

On the other hand, 1,3,4-oxadiazoles are an important group of heterocyclic compounds that have been known to posses a wide range of pharmacological properties (Zarghi and Hajimahdi 2013; Salahuddin et al. 2017; Lelyukh et al. 2020a, 2020b) including anticancer profile (Khan et al. 2013; Vaidya et al. 2021). Their antitumor properties can be expressed through different mechanisms featuring the affinity towards antiproliferation biotargets. For example, a series of novel heterocyclic azoles including 1,3,4-oxadiazole derivatives containing pyrazine moiety were evaluated for their anti-proliferative activity against the HEPG2 (human liver cancer cell), SW1116 (human colorectal carcinoma cell), HELA (human cervical cancer cell) and BGC823 (human gastric cancer). The results of molecular docking study suggested that such compounds may act as potential telomerase inhibitors (Zhang et al. 2012). Among benzotriazole substituted 1,3,4-oxadiazoles the highly active compoumd were identified which exhibited the most potent inhibitory action for FAK (focal adhesion kinase) with IC_{50} value of 1.2 ± 0.3 μM, which was comparable to the positive control cisplatin, and good activity against human breast cancer cell MCF-7 with IC_{50} value of 5.68 μg/ml, which was better than the reference drug cisplatin (Zhang et al. 2013). The antiproliferative activities of 5-aryl-1,3,4-oxadiazol/thiadiazol-2-ylamino-pyrimidine-5-carboxylic acid amides were investigated *in vitro* using histone deacetylase inhibitory assay and MTT assay. The results of the present studying shows that some oxadiazole derivatives displayed maximum HDAC inhibitory activity with an IC_{50} = 0.017 μM against HDAC-1 and an IC_{50} = 0.28 μM in HCT-116 cell proliferation assay (Rajak et al. 2011). It is observed that some 2,5-diaryl-1,3,4-oxadiazole linked pyrrolo[2,1-*c*][1,4]benzodiazepine conjugates exhibited significant anticancer activity against A2780, Gurav, MCF-7, Colo205, DWD cell lines with GI_{50} values ranging from <0.1 to 0.29 μM. The FACS analysis also showed more population in sub-G1 phase indicating that these conjugates have mitochondrial mediated apoptosis inducing ability (Kamal et al. 2010).

It is known that the conjugation of several pharmacologically attractive scaffolds is interesting and perspective approach for drug-like molecules build-up. In particular, various 4-thiazolidinone based hybrid molecules bearing 1,3,4-oxadiazole or relative heterocyclic systems has shown synergistic effect in many cases (Bondock et al. 2012; Bhutani et al. 2019; Omar et al. 2020; Lelyukh et al. 2022a). Based on this hypothesis, we presented the design and synthesis of novel 2-(2,4-dioxothiazolidine-3-yl)-acetamides containing 1,3,4-oxadiazole moiety and their 5-aryl/heterylidene derivatives for further screening of their anticancer activity *in vitro*.

Experimental part

Materials and methods

All reagents and solvents were of analytical grade, commercially available and used without further purification and drying. The starting 5-aryl-1,3,4-oxadiazole-2-amines were obtained according to known methodologies (Rajak et al. 2008).

Melting points were measured on a NAGEMA-K8 polarization microscope equipped with a Boetius heating stage using a digital thermometer «Ama-digit ad 14 th» and are uncorrected. The ^{1}H NMR spectra were recorded on Varian Gemini 400 MHz in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm units with use of δ scale. The elemental analyses (C, H, N) were performed using Elementar Vario L cube instrument. Analyses indicated by the symbols of the elements or functions were within ±0.4% of the theoretical values.

Chemistry

General procedure for the synthesis of 2-chloro-N-(5-aryl-[1,3,4]oxadiazol-2-yl)-acetamides ***2a-b***. To a mixture of 5-(4-methoxyphenyl)- (**1a**) or 5-(4-chlorophenyl)-2-amino-[1,3,4]oxadiazole (**1b**) (0.03 mol) and triethylamine (0.03 mol) in 50 ml dioxane an equimolar amount of chloroacetyl chloride (0.03 mol) was slowly added dropwise. Later the rection mixture was heated to 85–90 °C during 20 min, cooled and poured water (200 ml). Obtained powder was filtered off, washed with water, dried and recrystallized with acetic acid.

*2-Chloro-N-(5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl)-acetamide (**2a**).* Yield 90%; m.p. = 181–182 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.10 (s, 1H, CONH), 7.87 (d, 2H, *J* = 8.6 Hz, arom), 7.06 (d, 2H, *J* = 8.6 Hz, arom), 4.32 (s, 2H, $ClCH_2CO$), 3.87 (s, 3H, OCH_3). Calcd for $C_{11}H_{10}ClN_3O_3$: C, 49.36; H, 3.77; N, 15.70. Found: C, 49.51; H, 3.84; N, 15.82.

*2-Chloro-N-(5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl)-acetamide (**2b**).* Yield 91%; m.p. = 202–203 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.28 (s, 1H, CONH), 7.93 (d, 2H, *J* = 8.5 Hz, arom), 7.68 (d, 2H, *J* = 8.5 Hz, arom), 4.45 (s, 2H, $ClCH_2CO$). Calcd for $C_{10}H_7Cl_2N_3O_2$: C, 44.14; H, 2.59; N, 15.44. Found: C, 44.26; H, 2.67; N, 15.53.

General procedure for the synthesis of 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)-N-(5-aryl-[1,3,4]oxadiazol-2-yl)-acetamides ***3a-k***. A mixture of compounds **2a** or **2b** (3 mmol) with appropriate 5-arylidene-2,4-dioxothiazolidine potassium salt was heated under the reflux for 3h in 2 ml DMF/ethanol mixture (1:1). The powder obtained after cooling was filtered off, washed with ethanol, water and ethanol again, dried and recrystallized with DMF:ethanol (1:2) mixture.

*2-(5-Benzylidene-2,4-dioxothiazolidin-3-yl)-N-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3a**).* Yield 68%; m.p. = 243–244 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.40 (brs, 1H, CONH), 7.95 (s, 1H, -CH=), 7.84 (d, 2H, *J* = 7.9 Hz, arom), 7.69–7.65 (m, 2H, arom), 7.57–7.50 (m, 3H, arom), 7.12 (d, 2H, *J* = 7.6 Hz, arom), 4.65 (s, 2H, N^3-CH_2CO), 3.83 (s, 3H, OCH_3). Calcd for $C_{21}H_{16}N_4O_5S$: C, 57.79; H, 3.70; N, 12.84. Found: C, 57.93; H, 3.81; N, 12.97.

*2-[5-(4-Methylbenzylidene)-2,4-dioxothiazolidin-3-yl]-N-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3b**).* Yield 90%; m.p. = 181–182 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.40 (brs, 1H, CONH), 7.96 (s, 1H, -CH=), 7.84 (d, 2H, *J* = 7.5 Hz, arom), 7.55 (d, 2H, *J* = 7.3 Hz, arom), 7.37 (d, 2H, *J* = 6.7 Hz, arom), 7.12 (d, 2H, *J* = 7.3 Hz, arom), 4.64 (s, 2H, N^3-CH_2CO), 3.83 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3). Calcd for $C_{22}H_{18}N_4O_5S$: C, 58.66; H, 4.03; N, 12.44. Found: C, 58.78; H, 4.11; N, 12.57.

*2-[5-(4-Methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]-N-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3c**).* Yield 78%; m.p. = 234–235 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.40 (brs, 1H, CONH), 7.95 (s, 1H, -CH=), 7.84 (d, 2H, *J* = 8.5 Hz, arom), 7.63 (d, 2H, *J* = 8.4 Hz, arom), 7.12 (d, 4H, *J* = 8.4 Hz, arom), 4.64 (s, 2H, N^3-CH_2CO), 3.83 (s, 6H, 2*OCH_3). Calcd for $C_{22}H_{18}N_4O_6S$: C, 56.65; H, 3.89; N, 12.01. Found: C, 56.73; H, 3.96; N, 11.94.

*2-[5-(3,4-Dimethoxybenzylidene)-2,4-dioxothiazolidin-3-yl]-N-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3d**).* Yield 74%; m.p. = 206–207 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.39 (brs, 1H, CONH), 7.94 (s, 1H, -CH=), 7.83 (d, 2H, *J* = 7.8 Hz, arom), 7.24 (s, 1H, arom), 7.15–7.11 (m, 3H, arom), 4.64 (s, 2H, N^3-CH_2CO), 3.82 (s, 9H, 3*OCH_3). Calcd for $C_{23}H_{20}N_4O_7S$: C, 55.64; H, 4.06; N, 11.28. Found: C, 55.79; H, 4.14; N, 11.41.

*2-[5-(4-Chlorobenzylidene)-2,4-dioxothiazolidin-3-yl]-N-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3e**).* Yield 76%; m.p. > 260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.41 (brs, 1H, CONH), 8.00 (s, 1H, -CH=), 7.84 (d, 2H, *J* = 8.6 Hz, arom), 7.68 (d, 2H, *J* = 8.4 Hz, arom), 7.62 (d, 2H, *J* = 8.5 Hz, arom), 7.12 (d, 2H, *J* = 8.6 Hz, arom), 4.65 (s, 2H, N^3-CH_2CO), 3.82 (s, 3H, OCH_3). Calcd for $C_{21}H_{15}ClN_4O_5S$: C, 53.56; H, 3.21; N, 11.90. Found: C, 53.69; H, 3.27; N, 12.03.

*2-(5-Benzylidene-2,4-dioxothiazolidin-3-yl)-N-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3f**).* Yield 64%; m.p. > 260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.50 (s, 1H, CONH), 8.02 (s, 1H, -CH=), 7.92 (d, 2H, *J* = 8.5 Hz, arom), 7.68–7.65 (m, 4H, arom), 7.59–7.50 (m, 3H, arom), 4.68 (s, 2H, N^3-CH_2CO). Calcd for $C_{20}H_{13}ClN_4O_4S$: C, 54.49; H, 2.97; N, 12.71. Found: C, 54.62; H, 3.08; N, 12.84.

*2-[5-(4-Methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]-N-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3g**).* Yield 61%; m.p. = 254–255 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.49 (s, 1H, CONH), 7.97 (s, 1H, -CH=), 7.92 (d, 2H, *J* = 8.5 Hz, arom), 7.68–7.63 (m, 4H, arom), 7.13 (d, 2H, *J* = 8.7 Hz, arom), 4.66 (s, 2H, N^3-CH_2CO), 3.84 (s, 3H, OCH_3). Calcd for $C_{21}H_{15}ClN_4O_5S$: C, 53.56; H, 3.21; N, 11.90. Found: C, 53.70; H, 3.32; N, 11.83.

*2-[5-(3,4-Dimethoxybenzylidene)-2,4-dioxothiazolidin-3-yl]-N-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3h**).* Yield 68%; m.p. = 241–242 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.50 (brs, 1H, CONH), 7.96 (s, 1H, -CH=), 7.91 (d, 2H, *J* = 8.6 Hz, arom), 7.66 (d, 2H, *J* = 8.6 Hz, arom), 7.27–7.25 (m, 2H, arom), 7.15 (d, 1H, *J* = 9.0 Hz, arom), 4.66 (s, 2H, N^3-CH_2CO), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3). Calcd for $C_{22}H_{17}ClN_4O_6S$: C, 52.75; H, 3.42; N, 11.18. Found: C, 52.87; H, 3.51; N, 11.27.

*2-[5-(4-Chlorobenzylidene)-2,4-dioxothiazolidin-3-yl]-N-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3i**).* Yield 73%; m.p. > 260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.46 (s, 1H, CONH), 8.01 (s, 1H, -CH=), 7.92 (d, 2H, *J* = 8.4 Hz, arom), 7.70–7.62 (m, 6H, arom), 4.68 (s, 2H, N^3-CH_2CO). Calcd for $C_{20}H_{12}Cl_2N_4O_4S$: C, 50.54; H, 2.54; N, 11.79. Found: C, 50.67; H, 2.63; N, 11.86.

*2-[5-(4-Diethylaminobenzylidene)-2,4-dioxothiazolidin-3-yl]-N-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3j**).* Yield 62%; m.p. = 257–258 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.48 (s, 1H, CONH), 7.87 (d, 2H, *J* = 8.3 Hz, arom), 7.79 (s, 1H, -CH=), 7.60 (d, 2H, *J* = 8.2 Hz,

arom), 7.45 (d, 2H, *J* = 8.6 Hz, arom), 6.79 (d, 2H, *J* = 8.7 Hz, arom), 4.64 (s, 2H, N^3-CH_2CO), 3.42 (q, 4H, 2*CH_2CH_3), 1.12 (t, 6H, *J* = 6.8 Hz, 2*CH_2CH_3). Calcd for $C_{24}H_{22}ClN_5O_4S$: C, 56.30; H, 4.33; N, 13.68. Found: C, 56.48; H, 4.45; N, 13.79.

*2-[5-(4-Nitrobenzylidene)-2,4-dioxothiazolidin-3-yl]-N-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**3k**).* Yield 73%; m.p. > 260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.46 (brs, 1H, CONH), 8.36 (d, 2H, *J* = 8.6 Hz, arom), 8.12 (s, 1H, -CH=), 7.92 (d, 4H, *J* = 8.3 Hz, arom), 7.65 (d, 2H, *J* = 8.4 Hz, arom), 4.70 (s, 2H, N^3-CH_2CO). Calcd for $C_{20}H_{12}ClN_5O_6S$: C, 49.44; H, 2.49; N, 14.41. Found: C, 49.57; H, 2.61; N, 14.54.

*General procedure for the synthesis of 5-unsubstituted 2-(2,4-dioxothiazolidin-3-yl)-N-(5-aryl-[1,3,4]oxadiazol-2-yl)-acetamides **4a-b***. A mixture of the 2,4-dioxo-thiazolidine (20 mmol) and potassium hydroxide (20 mmol) in ethanol medium (20 ml) was heated under the reflux for 15 min. To the formed solution the appropriate 2-chloro-*N*-(5-aryl-1,3,4-oxadiazol-2-yl)-acedamide **2a** or **2b** and the few crystals of a potassium iodide as catalyst were added and then the reaction mixture was refluxed for 4 hours. The product obtained as a precipitate after cooling was filtered off, washed with water and methanol, dried and recrystallized with DMF:ethanol (1:2) mixture.

*2-(2,4-Dioxothiazolidin-3-yl)-N-[5-(4-methoxyphenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**4a**).* Spectral and analytical data are described in (Lelyukh et al. 2015).

*2-(2,4-Dioxothiazolidin-3-yl)-N-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**4b**).* Yield 78%; m.p. = 234–235 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.47 (brs, 1H, CONH), 7.94 (d, 2H, *J* = 7.3 Hz, arom), 7.56 (d, 2H, *J* = 6.9 Hz, arom), 4.46 (s, 2H, N^3-CH_2CO), 4.26 (s, 2H, 5-CH_2, thiaz). Calcd for $C_{13}H_9ClN_4O_4S$: C, 44.26; H, 2.57; N, 15.88. Found: C, 44.39; H, 2.64; N, 15.79.

*General procedure for the synthesis of 2-(5-heterylidene-2,4-dioxothiazolidin-3-yl)-N-(5-aryl-[1,3,4]oxadiazol-2-yl)-acetamides **5a-c***. A mixture of compounds **4a** or **4b** (3 mmol), appropriate heterylcarbaldehyde (4 mmol) and anhydrous sodium acetate (3 mmol) in glacial acetic acid (20 ml) was heated under the reflux for 4h. The reaction mixture was cooled to room temperature, the obtained precipitate was filtered off, washed with acetic acid, water and methanol, dried and recrystallized with acetic acid or DMF:acetic acid (1:2) mixture.

*2-[5-(Pyridin-3-ylmethylene)-2,4-dioxothiazolidin-3-yl)-N-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**5a**).* Yield 58%; m.p. = 252–253 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.46 (brs, 1H, CONH), 8.89 (s, 1H, pyridine), 8.05–8.02 (m, 2H, -CH=, pyridine), 7.92 (d, 2H, *J* = 8.4 Hz, arom), 7.66 (d, 2H, *J* = 8.5 Hz, arom), 7.61–7.58 (m, 1H, pyridine), 4.69 (s, 2H, N^3-CH_2CO). Calcd for $C_{19}H_{12}ClN_5O_4S$: C, 51.65; H, 2.74; N, 15.85. Found: C, 51.79; H, 2.85; N, 15.93.

*2-[5-(Furan-2-ylmethylene)-2,4-dioxothiazolidin-3-yl)-N-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**5b**).* Yield 59%; m.p. = 252–253 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.40 (s, 1H, CONH), 8.09 (s, 1H, -CH=), 7.92 (d, 2H, *J* = 8.4 Hz, arom), 7.83 (s, 1H, furan), 7.65 (d, 2H, *J* = 8.4 Hz, arom), 7.18 (d, 1H, *J* = 3.3 Hz, furan), 6.78 (s, 1H, furan), 4.65 (s, 2H, N^3-CH_2CO). Calcd for $C_{18}H_{11}ClN_4O_5S$: C, 50.18; H, 2.57; N, 13.00. Found: C, 50.32; H, 2.68; N, 13.11.

*2-[5-(Thiophen-2-ylmethylene)-2,4-dioxothiazolidin-3-yl)-N-[5-(4-chlorophenyl)-[1,3,4]oxadiazol-2-yl]-acetamide (**5c**).* Yield 62%; m.p. = 236–237 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 12.44 (s, 1H, CONH), 8.29 (s, 1H, -CH=), 8.08 (d, 1H, *J* = 4.7 Hz, thiophene), 7.92 (d, 2H, *J* = 7.8 Hz, arom), 7.77 (s, 1H, thiophene), 7.66 (d, 2H, *J* = 8.1 Hz, arom), 7.34–7.32 (m, 1H, thiophene), 4.66 (s, 2H, N^3-CH_2CO). Calcd for $C_{18}H_{11}ClN_4O_4S_2$: C, 48.38; H, 2.48; N, 12.54. Found: C, 48.52; H, 2.57; N, 12.67.

Pharmacology

Anticancer activity against 60 human tumor cell lines

A primary anticancer assay was performed at approximately sixty human tumor cell lines panel derived from nine neoplastic diseases, in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda (Boyd and Paull 1995; Monks et al. 1991; Shoemaker 2006). The tested compounds were added to the culture at a single concentration (10^{-5}M) and cultures were incubated for 48 h. Endpoint determinations were made with a protein binding dye, sulforhodamine B (SRB). Results for each tested compound were reported as the growth percent of the treated cells when compared to the untreated control cells. Growth percent was evaluated spectrophotometrically versus controls not treated with the test agents. The cytotoxic and/or growth inhibitory effects of the most active selected compounds were tested *in vitro* against the full panel of about 60 human tumor cell lines at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8}M. The 48-h continuous drug exposure protocol was followed and an SRB protein assay was used to estimate cell viability or growth.

Using the seven absorbance measurements [time zero, (Tz), control growth in the absence of drug, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the growth percent was calculated at each of the drug concentrations levels. Percent of growth inhibition was calculated as follows:

$$[(Ti - Tz)/(C - Tz)] \times 100 \text{ for concentrations for which } Ti \geq Tz$$

$$[(Ti - Tz)/Tz] \times 100 \text{ for concentrations for which } Ti < Tz.$$

Three dose-response parameters were calculated for each compound. Growth inhibition of 50% (GI_{50}) was calculated according to the following equation:

$$[(Ti - Tz)/(C - Tz)] \times 100 - 50,$$

which is the drug concentration resulting in a 50% lower net protein increase in the treated cells (measured by SRB

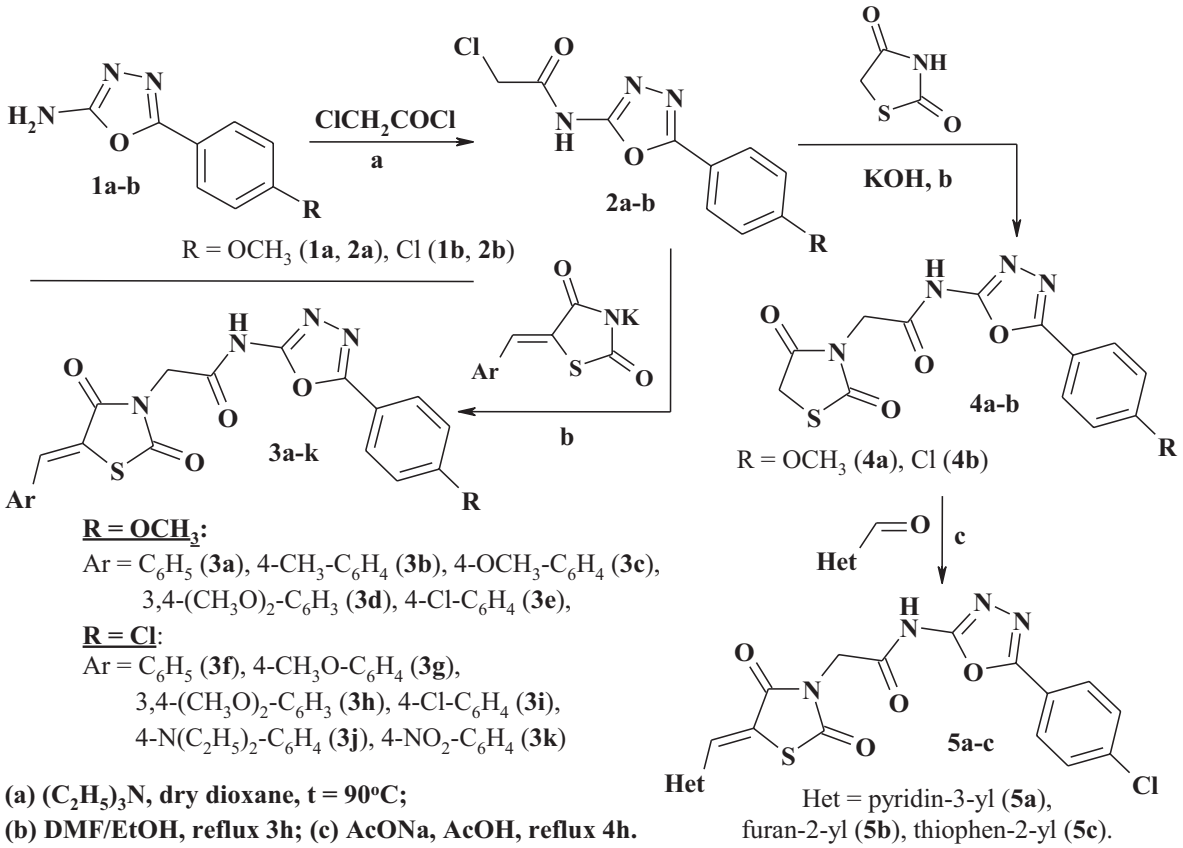
staining) as compared to the net protein increase seen in the control cells. The drug concentration resulting in total growth inhibition (TGI) was calculated from Ti = Tz. The LC_{50} (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment was calculated from [(Ti – Tz)/Tz] × 100 = -50. Values were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the value for that parameter was expressed as more or less than the maximum or minimum concentration was tested.

Results and discussion

Chemistry

The starting 5-aryl-1,3,4-oxadiazole-2-amines synthesized using known methods (Rajak et al. 2008) easily reacted with chloroacetyl chloride in dioxane medium yielding 2-chloro-*N*-(5-aryl-[1,3,4]oxadiazol-2-yl)-acetamides **1a** and **1b**. Due to the established an essential influence of the nature of 5-ylidene moiety in the 4-thiazolidinone cycle on the antitumor activity (Abumelha and Saeed 2020; Patil et al. 2010) further transformations were aimed at the interaction of compounds **1a** and **1b** with potassium salts of 5-arylidene-2,4-dioxothiazolidine derivatives. Using this approach the synthesis of target 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)-*N*-(5-aryl-[1,3,4]oxadiazol-2-yl)-acetamides **3a-k** was performed. Their 5-unsubstituted analogues **4a-b** were obtained *via N*-alkylation reaction between 2-chloro-*N*-(5-aryl-1,3,4-oxadiazol-2-yl)-acedamides **1a-b** and the generated *in situ* 2,4-thiazolidinedione potassium salt (Scheme 1). In addition, the obtained oxadiazolyl-thiazolidinones **4a-b** were modified by interaction with pyridine-3-carbaldehyde, furfural or thiophene-2-carbaldehyde according to the standard Knoevenagel condensation procedure (medium – acetic acid, catalyst – fused sodium acetate) forming the corresponding 5-heterylidene derivatives **5a-c** according to the Scheme 1.

Structures of all synthesized compounds were confirmed by ^{1}H NMR spectroscopy and elemental analysis. In ^{1}H-NMR spectra, the signals for the protons of all the structural units were observed in their characteristic ranges. In particular, the protons of the chloroacetamide $ClCH_2CO$ fragment for compounds **2a-b** appeared as singlet at δ ~ 4.32–4.45 ppm. In the ^{1}H NMR spectra of the 5-unsubstituted derivatives **4a-b** two singlets in the range of δ ~ 4.26–4.33 and δ ~ 4.46–4.47 ppm corresponding to cyclic methylene group and N^3-CH_2CO fragments had been observed. Instead, the protons of the N^3-CH_2CO fragment of 5-aryl/heterylidene derivatives (compounds **3a-k** and **5a-c**) resonates as singlet in the range of δ ~ 4.64–4.70 ppm.



Scheme 1. Synthesis of 2-(2,4-dioxothiazolidin-3-yl)-*N*-(5-aryl-[1,3,4]oxadiazol-2-yl)-acetamides and their 5-aryl/heterylidene derivatives

The signal of a methylidene proton –CH= for the compounds **3a-k** and **5a-c** appears as singlet with a higher chemical shift in the range of δ ~ 7.79–8.29 ppm. According to the literature data, that indicates a *Z*-configuration of the exocyclic C=C bond at the 5-arylidene fragment and, respectively, only Z-isomers were obtained (Popov-Pergal et al. 1991; Bruno et al. 2002). Such displacement of the methylidene proton in a weak magnetic field due to the deshielding effect of the adjacent C=O, than it would do in *E*-isomers, because of the lower deshielding effect of 1-S (Vicini et al. 2008). For NH proton of the amide CONH fragment a singlet or broad singlet in the range of δ ~ 12.39–12.50 ppm had been observed.

Evaluation of anticancer activity *in vitro*

The synthesized oxadiazole-thiazolidinone hybrids **3b-e** and **4a-b** were selected by the National Cancer Institute (NCI) and evaluated at the single concentration of 10^{-5} M towards panel of the approximately sixty cancer cell lines. The human tumor cell lines were derived from the nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers. Primary anticancer assays were performed according to the Developmental Therapeutic Program protocol (www.dtp.nci.nih.gov), which was described elsewhere (Monks et al. 1991; Boyd and Paull 1995; Boyd and Teicher 1997; Shoemaker 2006).

Table 1. Anticancer screening data of the tested compounds in 1-dose concentration 10^{-5} M.

Compound	Mean growth, %	Range of growth, %	The most sensitive cell lines	Growth of the most sensitive cell line, %
3b	104.13	85.97 ÷ 124.46	HL-60(TB) (*Leukemia*)	85.97
			UO-31 (*Renal Cancer*)	86.30
			A498 (*Renal Cancer*)	86.50
			MCF7 (*Breast Cancer*)	93.75
3c	107.06	84.34 ÷ 123.26	UO-31 (*Renal Cancer*)	84.34
			MOLT-4 (*Leukemia*)	92.36
			NCI-H322M (*NSC Lung Cancer*)	93.17
3d	101.83	66.67 ÷ 129.14	UO-31 (*Renal Cancer*)	66.67
			CAKI-1 (*Renal Cancer*)	68.49
			HCT-15 (*Colon Cancer*)	76.86
			NCI/ADR-RES (*Ovarian Cancer*)	83.26
			LOX IMVI (*Melanoma*)	86.27
			MALME-3M (*Melanoma*)	86.72
			HL-60(TB) (*Leukemia*)	90.95
			NCI-H322M (*NSC Lung Cancer*)	91.39
			SNB-75 (*CNS Cancer*)	92.83
3e	101.86	76.85 ÷ 123.75	MOLT-4 (*Leukemia*)	76.85
			UO-31 (*Renal Cancer*)	79.68
			K-562 (*Leukemia*)	79.84
			A498 (*Renal Cancer*)	80.07
			HL-60(TB) (*Leukemia*)	80.90
			SR (*Leukemia*)	81.66
			CAKI-1 (*Renal Cancer*)	87.62
			MCF7 (*Breast Cancer*)	89.51
			HOP-92 (*NSC Lung Cancer*)	91.84
4a	103.56	74.37 ÷ 116.38	A498 (*Renal Cancer*)	74.37
			UO-31 (*Renal Cancer*)	84.78
			SNB-75 (*CNS Cancer*)	90.91
			HOP-92 (*NSC Lung Cancer*)	90.92
4b	99.34	74.06 ÷ 122.65	UO-31 (*Renal Cancer*)	74.16
			MALME-3M (*Melanoma*)	82.28
			UACC-257 (*Melanoma*)	86.31
			SNB-75 (*CNS Cancer*)	88.58
			OVCAR-5 (*Ovarian Cancer*)	88.90
			NCI-H226 (*NSC Lung Cancer*)	89.34

The primary anticancer screening results are reported as the cancer cell line growth percent (GP) and are presented in Table 1. Range of growth (%) showed the lowest and the highest growth that was found among different cancer cell lines.

The tested *N*-5-aryl-1,3,4-oxadiazole substituted 2-(2,4-dioxothiazolidin-3-yl)- acetamides **4a-b** and their 5-arylidene derivatives **3b-e** displayed a weak to medium in the *in vitro* screening on the cancer cell lines. However a selective influence of tested compounds on several cancer cell lines was observed (Table 1). In particular, some compounds were more active compared to their average values against renal cancer CAKI-1 cell line (**3d,** GP = 68.49%), colon cancer HCT-15 cell line (**3d,** GP = 76.86%), renal cancer A498 cell line (**4a,** GP = 74.37%). Compound **3e** showed a selective effect on some leukemia lines (MOLT-4, K-562, HL-60(TB) and SR) with a range of GP values within 76.85÷81.66%. In addition, a renal cancer UO-31 cell line turned out to be the most sensitive cell line to the action of all compounds (GP = 66.67 ÷ 86.30%). It should also be noticed that the average group activity of this compounds was lower than previously described 1,3,4-oxadiazole based 2-iminothiazolidin-4-ones (Lelyukh et al. 2022b).

Conclusions

In our work, we presented the synthesis and anticancer activity evaluation a series of novel 1,3,4-oxadiazole containing 2-(2,4-dioxothiazolidin-3-yl)-acetamides. It is shown that the proposed synthetic approach, which includes acylation, N-alkylation and Knevenagel condensation reactions, provides the sufficient possibility to design 4-thiazolidinone and 1,3,4-oxadiazole hybrid molecules. Synthesized compounds **3b-e** and **4a-b** were tested and some of them displayed moderate antitumor activity against leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancer cell lines. The current results can be considered as background for further optimization and rational design in the 1,3,4-oxadiazole substituted 4-thiazolidinones area to improve their pharmacological characteristics including antitumor quality.

Acknowledgments

We are grateful Drug Synthesis and Chemistry Branch, National Cancer Institute, Bethesda, MD, USA, for *in vitro* evaluation of the anticancer activity.

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