Synthesis, in vitro antiproliferative and antimycobacterial activity of thiazolidine-2,4-dione and hydantoin derivatives

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New 2H-chromene derivatives bearing thiazolidine-2,4-dione or hydantoin moieties were synthesized and the structures were confirmed by 1H NMR and 13C NMR as well as 2D NMR, FTIR and HR-ESI-MS spectra. The compounds were evaluated for their in vitro cytotoxicity against four human cancer cell lines, namely HL-60 (acute promyelocyte leukemia), REH (lymphoid leukemia), K-562 (chronic myeloid leukemia) and EJ (urinary bladder carcinoma). The 2H-chromene derivative containing thiazolidine-2,4-dione ring 5 was potent against a panel of three cancer cell lines, with an IC50 in the range of 13.1-39.6 μM and exhibited pronounced antiproliferative activity against lymphoid leukemia (REH cell line) with an IC50 value of 13.1 μM. The hydantoin containing 2H-chromene derivative 7 having an IC50 value of 83.7 μM was highly effective against chronic myeloid leukemia K-562. Compounds 5 and 7 also demonstrated significant antimycobacterial activity against Mycobacterium tuberculosis H37Rv strain with minimum inhibitory concentration (MIC) ranging from 0.29 and 0.36 μM, respectively.

Keywords: Antiproliferative/cytotoxic effects, Antimycobacterial activity, 2H-Chromene, Hydantoin, Thiazolidine-2,4-dione.

INTRODUCTION

The hydantoin (1,3-imidazolidinedione) derivatives [1] and thiazolidinediones (thiazolidine-2,4-diones) [2, 3] exhibit a plethora of biochemical and pharmacological activities. The thiazolidinediones (TZDs) have been characterized as a new dawn in cancer chemotherapy with a broad spectrum of cytotoxicity towards different human cancer cells [4, 5]. It is well known that TZDs exert their anti-diabetic effects through a mechanism that involves activation of PPARγ receptor. The wide spectrum of PPARγ activation effects may also be beneficial in the treatment of different types of cancer [6]. Thus, several new drugs such as efatutazon, netoglitazone, rosiglitazone and troglitazone (Fig. 1), exhibit their anticancer activity via PPARγ-dependent or -independent signaling pathways [7]. In the meantime, the antitumor effect of hydantoin derivatives has been reported by a number of authors (Fig. 1). Some of hydantoin derivatives, characterized by a 1-phenethyl and a 5-(E)-benzylidene substituents, inhibit EGFR autophosphorylation and polyGAT phosphorylation, as well as inhibit the growth and proliferation of human A431 cells, which overexpress EGFR [8] (Fig. 1). The hydantoin derivatives tested by Rajic et al., showed rather marked inhibitory activity against HeLa and MCF-7 cell lines, and no cytotoxic effects on normal cells [9]. The anti-cancer potential of 5-benzylidene-hydantoins demonstrating its relation to SIRT inhibition was proved by Lionel et al. [10]. Mudit et al., [11] described phenylmethylene hydantoins, as a novel antimitastatic lead class with the potential to control metastatic prostate cancer. The compounds synthesized by Reddy et al., [12] contain an N-benzylindole nucleus linked to a hydantoin moiety via a double bond with Z-geometry were described as potential anticancer agents for the treatment of breast cancer. 5-[(1H-indol-3-ylmethyl)-2-thiohydantoins and 5-[(1H-indol-3-ylmethyl)hydantoins were found to be potent necrostatins [13]. In addition, (Z)-5-(4-hydroxybenzylidene)-imidazolidine-2,4-dione display moderate antiproliferative activity against the human cervical carcinoma (HeLa) cell line [14].

On the other hand, many studies have shown that azole heterocycles such as thiazolidine-2,4-dione and imidazolidine-2,4-dione are useful pharmacophores possessing antimycobacterial activity [15]. There have been reports on some thiazolidine-2,4-dione derivatives [16] and various imidazolidine-2,4-dione derivatives [17, 18], evaluated in the primary assay for antimycobacterial activity which exhibit

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remarkable growth inhibitory activity towards *M. Tuberculosis*. Also, 2-substituted 2H-chromenes have wide range of applications [19] as antimycobacterial [20] and antitumor agents [21], inclusive. Therefore, our hypothesis is that chromenyl thiazolidines and hydantoin derivatives might have a broad spectrum of pharmacological activities as well as selective cytotoxicity against cancer cell lines. Continuing the research on the biological activity of 2H-chromene derivatives, now we present the synthesis of compounds that comprise a 2H-chromene scaffold and thiazolidine-2,4-dione or imidazolidine-2,4-dione heterocyclic rings. Herein we also report on the *in vitro* screening against *M. Tuberculosis* H37Rv as well as antiproliferative/cytotoxic effects of the newly synthesized compounds in a panel of human tumor cell lines.

EXPERIMENTAL

General

The IR spectra were recorded on a Nicolet iS10 FT-IR Spectrometer from Thermo Scientific (USA) using an ATR technique. The NMR experiments on a Bruker Avance II+ 600 MHz NMR spectrometer in DMSO-*d*$_6$ allowed the assignment of the structures. The precise assignment of the $^1$H and $^{13}$C NMR spectra (resolved signals) was accomplished by measurements of 2D homonuclear correlation (COSY), DEPT-135 and 2D inverse detected heteronuclear (C–H) correlations (HMOC and HMBC) and NOESY. HR-ESI-MS spectra were recorded on an LTQ Orbitrap Discovery® spectrometer (ThermoFisher, Germany) equipped with electrospray ionization module Ion Max® (ThermoScientific, USA) operating in positive mode. The melting points were determined using a Buchi 535 apparatus. For TLC was used silica gel 60 GF254 Merck pre-coated aluminum sheets, eluted by hexane-chloroform-acetone 5:3:2 (vol. parts). All reagents were purchased from E. Merck (Darmstadt, Germany) and Aldrich (Milwaukee, MI, USA).

![Fig. 1. Representative examples of 2H-chromene, thiazolidinedione and hydantoin derivatives with anticancer activity and rationale for the designed target compounds.](image-url)
SYNTHESIS

2-Methyl-2H-chromene-3-carbaldehyde 3a was obtained according to the literature [20]. Yield 0.70 g (57 %), yellow oil. HRMS (ESI) m/z: Calcd. [M+H]+ 175.0753; Found [M+H]+ 175.07527.

2-Phenyl-2H-chromene-3-carbaldehyde 3b was synthesized according to the literature [23] with modifications. In a typical example, 3.19 ml (3.3 g, 25 mmol) cinnamaldehyde, 3.05 ml (3.05 g, 25 mmol) salicylaldehyde, benzoic acid (0.61 g, 5 mmol) and pyrrolidine (0.41 ml, 5 mmol) were dissolved in 100 ml toluene. The reaction was stirred vigorously at 25 oC for 20 hours. The reaction was monitored by thin layer chromatography. The solution was filtered and toluene evaporated on a rotary evaporator at elevated temperature. The residue was dissolved in 5 ml of CHCl3 and 5 ml hexane, and filtered over 15 g silica gel with eluent hexane-EtOAc mixture 10:1. After eluent evaporation, yellow crystals of the final compound 3b were obtained. Yield 60%, 3.36 g; yellow crystals; m.p. 75-77 °C; lit. m.p. (23) 75-76 °C. 1HNMR (600 MHz, DMSO-d6, ppm) δ: 6.257 (s, 1H, H-2), 6.86 (d, J = 8.2 Hz, 1H, H-9), 6.996 (dt, J = 1.1, 7.5 Hz, 1H, H-7), 7.28-7.31 (m, 5H, Ph), 7.324 (ddd, J = 1.6, 7.4, 8.2 Hz, 1H, H-8), 7.457 (dd, J = 1.6, 7.5 Hz, 1H, H-6), 7.897 (s, 1H, H-4), 9.673 (s, 1H, CHO). 13CNMR (150 MHz, DMSO-d6, ppm) δ: 73.63 (C-2), 117.21 (C-9), 120.65 (C-5), 122.44 (C-7), 127.30 (o-Ph), 129.05 (m-Ph), 129.15 (p-Ph), 130.27 (C-6), 133.51 (C-3), 134.12 (C-8), 139.12 (p-Ph), 141.78 (C-4), 154.30 (C-10), 191.56 (CHO). HRMS(ESI) m/z found: 237.09076 [M+H]+; calcd. for C10H13O2: 237.09106 [M+H]+.

(Z,s-cis)-5-[(2-Methyl-2H-chromene-3-yl)methylene]-1,3-thiazoline-2,4-dione 5. 1,3-Thiazoline-2,4-dione 4 (3 mmol, 0.35 g) and 2-methyl-2H-chromene-3-carbaldehyde 3 (3 mmol, 0.52 g) were dissolved in abs. ethanol (15 ml). The solution was refluxed for 8 h in the presence of a small amount of piperidine (0.2 ml) as a catalyst. These cell lines have been well validated in our laboratory as a proper test system for platinum agents. The RJ cell line was obtained from the unit of Toxicology and Chemotherapy at the Deutsches Krebsforschungszentrum. The other cell lines were obtained from DSMZ German Collection of Microorganisms and Cell Cultures.
The cell culture flasks and the 96-well microplates were obtained from NUNCLON (Denmark). The stock solutions of the tested compounds (10 mM) were freshly prepared in DMSO. The serial dilutions of the tested compounds were prepared immediately before use. After the final dilutions, the obtained concentrations of DMSO never exceeded 1%. Cytotoxicity of the compounds was assessed using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] dye reduction assay as described by Mossman [24] with some modifications [25]. Exponentially growing cells were seeded in 96-well microplates (100 IL/well at a density of 3.5/105 cells/mL for the adherent and 1/105 cells/mL for the suspension cell lines) and allowed to grow for 24 h prior the exposure to the studied compounds. The cells were exposed to the tested agents for 72 h, whereby a set of 8 separate wells was used for each concentration. Every test was run in triplicate. After incubation with the tested compounds MTT solution (10 mg/mL in PBS) aliquots were added to each well. The plates were further incubated for 4 h at 37 °C and the formazan crystals formed were dissolved by adding 110 IL of 5% HCOOH in 2-propanol. The MTT-formazan absorption was measured using a multimode microplate reader (Beckman Coulter DTX880) and the results were normalized as a percentage of the untreated control (set as 100% viable). The MTT-bioassay data were normalized as a percentage of the untreated control (set as 100% viability), were fitted to sigmoidal dose response curves and the corresponding IC50 values (concentrations causing 50 % suppression of cellular viability) were calculated using non-linear regression analysis (Curve-fir; GraphPad Prism software for PC).

The cell lines were purchased from the DSMZ GmbH, (Braunschweig, Germany). They were cultured under standard conditions - RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) and 2 mM L-glutamine - in cell culture flasks housed at 37 °C in an incubator, BB16-Function Line’ Heraeus (Kendro, Germany) with humidified atmosphere and 5 % of CO2. The cell cultures were maintained in log phase by supplementation with fresh medium two or three times weekly.

Antimycobacterial activity. The antimycobacterial activity was determined towards reference strain M. Tuberculosis H37Rv through the proportional method of Canetti [26]. This method, recommended by WHO, is the one most used worldwide for exploration of sensitivity/resistance of tuberculosis strains towards chemotherapeutics. It allows precise determination of the proportion of mutants resistant to a certain drug. A sterile suspension/solution of the tested compound was added to Löwenstein-Jensen based medium before its coagulation (30 min at 85 °C). The compound was tested at four concentrations – 2 µg/ml, 0.2 µg/ml, 0.1 µg/ml and 0.05 µg/ml, (in DMSO). Tubes with Löwenstein-Jensen medium (5 ml) containing the tested compounds and those without them (controls) were inoculated with a suspension of M. tuberculosis H37Rv (105 cells/ml) and incubated for 45 days at 37 °C. The ratio between the number of colonies of M. tuberculosis grown in medium containing the compounds and the number of colonies in the control medium were calculated and expressed as a percentage of inhibition. The cell culture flasks and the 96-well microplates were obtained from NUNCLON (Denmark). The stock solutions of the tested compounds (10 mM) were freshly prepared in DMSO. The serial dilutions of the tested compounds were prepared immediately before use. After the final dilutions the obtained concentrations of DMSO never exceeded 1%. Cytotoxicity of the compounds was assessed using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] dye reduction assay as described by Mossman [24] with some modifications [25]. Exponentially growing cells were seeded in 96-well microplates (100 IL/well at a density of 3.5/105 cells/mL for the adherent and 1/105 cells/mL for the suspension cell lines) and allowed to grow for 24 h prior the exposure to the studied compounds. Cells were exposed to the tested agents for 72 h, whereby a set of 8 separate wells was used for each concentration. Every test was run in triplicate. After incubation with the tested compounds MTT solution (10 mg/mL in PBS) aliquots were added to each well. The plates were further incubated for 4 h at 37 °C and the formazan crystals formed were dissolved by adding 110 µl solvent (5% HCOOH in 2-propanol). The MTT-formazan absorption was measured using a multimode microplate reader (Beckman Coulter DTX880) and the results were normalized as a percentage of the untreated control (set as 100% viable). The MTT-bioassay data were normalized as a percentage of the untreated control (set as 100% viability), were fitted to sigmoidal dose response curves and the corresponding IC50 values (concentrations causing 50 % suppression of cellular viability) were calculated using non-linear regression analysis (Curve-fir; GraphPad Prism software for PC).
The MIC was defined as the minimum concentration of the compound required to inhibit bacterial growth completely (0% growth). The MIC values were calculated and given as μM. Ethambutol and isoniazid were used as controls.

RESULTS AND DISCUSSION

Synthesis. The synthetic route for preparing the compounds was illustrated in Schemes 1 and 2. 2H-Chromene derivatives 3a,b were selected as starting compounds and were synthesized via Michael-aldol reaction, according to the known procedure [27] (Scheme 1). The reaction of 2-hydroxybenzaldehyde with α,β-unsaturated aldehydes under basic conditions afforded appropriate 2-substituted 2H-chromene-3-carbaldehyde 3a,b. The preparation of 2-methyl-2H-chromene-3-carbaldehyde 3a is conducted in 1,4-dioxane under reflux. For the synthesis 2-phenyl-2H-chromene-3-carbaldehyde 5 we used piperidine as a catalyst [23].

The new compound 5-[(2-methyl-2H-chromen-3-yl)methylidene]-1,3-thiazolidine-2,4-dione 5 was synthesized by Knoevenagel condensation of 2-methyl-2H-chromene-3-carbaldehyde 2a and 1,3-thiazolidine-2,4-dione 3 (Scheme 2).

Several conditions were tested (sodium acetate in acetic acid, sodium acetate in DMF and piperidine in ethanol/methanol under thermal conditions) for the preparation of 2-methylchromene - derivative 5, but the best result (a moderate yield of 44 %) was obtained by refluxing ethanol and in the presence of a catalytic amount of piperidine. As outlined in Scheme 2, when 2-phenyl-2H-chromene-3-carbaldehyde 5 reacted with hydantoin 6 under the selected conditions.

Scheme 1. Synthesis of 2-methyl-2H-chromene-3-carbaldehyde 3a and 2-phenyl-2H-chromene-3-carbaldehyde 3b through the domino oxa-Michael/aldol condensation reactions.

Scheme 2. Synthesis of 2-methylchromene derivative 5 and 2-phenylchromene derivative 7.
conditions, dehydration did not occur and the final product is intermediate alcohol 5-[hydroxy(2-phenyl-2H-chromen-3-yl)ethyl]imidazolidine-2,4-dione 7. Our efforts to obtain a Knoevenagel product after the condensation reaction under the conditions described above failed and suggested that other factors might influence the reaction.

The structures of novel compounds 5 and 7 were proven by means of FTIR, 1H, 13C NMR and HR-ESI-MS spectral methods and were confirmed additionally by extensive two-dimensional (2D) NMR (COSY, multiplicity-edited HSQC, HMBC) and NOESY spectra. In the 1H NMR in DMSO-d6 spectrum of product 5 the signal for CH2 protons in thiazolidinedione ring is absent and in addition to the aromatic protons of chromene ring (6.858-7.291 ppm), a sharp singlet due to vinyl proton is observed at 7.291 ppm. The 13C NMR spectrum of 2-methylchromene derivative 4 shows 13 signals. The signal for C-2 of chromene ring appears at 71.30 ppm, the vinyl proton resonates at 151.68 ppm and the signals for the carbonyl are observed at 167.22 and 167.49, respectively. Meanwhile, in the 1H NMR spectra of 2-methylchromene derivative 5 only a set of signals occurs what confirms that only one stereoisomer Z has been obtained during the condensation. That is in agreement with the literature [27] and isomer Z appears to be more thermodynamically stable than isomers E. The NOESY spectrum (Fig. 2) shows a NOE effect and proximity between the vinyl proton and H-2; and between the vinyl proton and CH3 protons. That proves the (s-cis)-conformation of the two conjugated double bonds. The described 2-methylchromene derivative 5 possessing a chiral center at C-2 position is a racemate.

In the 1H NMR spectrum of product 7 in DMSO-d6, there is no signal for CH2 protons in the hydantoin ring. In addition to the aromatic protons of chromene ring (6.630-7.372 ppm), a doublet of doublets at 4.200 for CH-NH and a broad doublet at 4.490 (J=5.2 Hz) for CHOH are observed. A doublet at 5.670 for the hydroxyl group with the same coupling constant of 5.2 Hz is registered. The lack of a cross peak for this signal in HSQC spectrum for OH proton indicates that there is not a carbon atom connected directly to it. Having localized the position of OH proton it is easy to assign the remaining protons from COSY spectrum. All carbon signals are assigned using HSQC and HMBC. The signal at 4.200 ppm is coupled by two small J constants (1.0 and 2.3 Hz). One of these constant is a J constant to the NH proton, the other is a gauche constant in the 4-substituted ethane structure. The infrared spectrum of 2-methylchromene derivative 5 shows a strong absorption at 1733 cm⁻¹ and 1678 cm⁻¹ corresponding to C=O functional groups, a band at 1607 cm⁻¹ (C=C stretching in chromene ring) and 1573 cm⁻¹ corresponding to C=C bond. The IR spectrum of compound 7 shows bands at 3227 cm⁻¹ (NH stretching), 1731 and 1698 cm⁻¹ (C=O functional groups) and 1603 cm⁻¹ (C=C stretching in chromene ring). In addition, the novel structures are supported by a positive HR-ESI-MS spectrum which reveals a molecular ion peak at m/z 274.05334 [M+H]⁺, (calcd. [M+H]⁺ 274.05324) and 337.11804 [M+H]⁺ (calcd. [M+H]⁺ 337.11823) and allows confirming the molecular formulas, C14H17NO5S and C9H16N2O3, of compounds 5 and 7, respectively.

**Antiproliferative/cytotoxic effects.** Table 1 summarizes the antiproliferative effects of 5-[2-Methyl-2H-chromen-3-yl)methylidene]-1,3-thiazolidine-2,4-dione and 5-[Hydroxy(2-phenyl-2H-1-benzopyran-3-yl)methyl]imidazolidine-2,4-dione against a panel of four human tumor cell lines, namely HL-60 (acute promyelocyte leukemia), REH (lymphoid leukemia), K-562 (chronic myeloid leukemia) and EJ (urinary bladder carcinoma), using the alkylating agent melphalan as a reference anticancer drug.

The results of the *in vitro* cytotoxicity bioassay indicated that the compounds 5 and 7 exerted moderate to potent growth inhibition against the tested cancer cells with IC₅₀ values of 13.1-98 μM. Compound 5 showed higher activity than compound 7 against HL-60, REH and EJ with the IC₅₀ values of 39.6, 13.1 and 26.2 μM, respectively. As for the activity against chronic myeloid leukemia K-562, the highest cytotoxic activity was displayed by compound 7 with IC₅₀ a value of 83.7 μM. Additionally, compound 5 was found to be more potent against REH tumor cell lines (IC₅₀ = 13.1 μM) than Melphalan. REH cells were the most sensitive to the studied compounds and the potency of the most active compounds is similar to that of Melphalan. EJ cells seem to be the most resistant to compound 7. However, compound 5 showed a relatively high antiproliferative potency toward EJ cells.
**Fig. 2.** Part of NOESY spectrum of 2-methylchromene derivative 5 showing the NOE effects between vinyl proton at 7.291 and 5.257 (H-2) ppm, and between 7.291 and 1.304 (CH₃) ppm, which confirms the (s-cis)-conformation.

**Table 1.** Cytotoxicity (IC₅₀) of the compounds 5 and 7 against different cell lines and antimycobacterial activity against reference strain *Mycobacterium tuberculosis* H37Rv.

<table>
<thead>
<tr>
<th>Compd</th>
<th>Structure</th>
<th>IC₅₀ (μM)</th>
<th>MIC (μM)</th>
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<tr>
<td></td>
<td></td>
<td>HL-60²</td>
<td>K-562³</td>
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<tr>
<td>5</td>
<td></td>
<td>39.6 ± 2.7</td>
<td>98.0 ± 3.9</td>
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<td>7</td>
<td></td>
<td>73.2 ± 4.8</td>
<td>83.7 ± 3.6</td>
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<tr>
<td>Melphalan⁷</td>
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<td>11.2 ± 1.9</td>
<td>28.3 ± 3.2</td>
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<tr>
<td>EMB_2HCl⁸</td>
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<td>INH⁹</td>
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¹Means±sd from eight independent experiments. Cell line: ²HL-60 (acute promyelocyte leukemia), ³K-562 (chronic myeloid leukemia), ⁴REH (lymphoid leukemia) and ⁵EJ (urinary bladder carcinoma); ⁶reference strain of *Mycobacterium tuberculosis* H37Rv, MIC (μM) was defined as the lowest concentration resulting in a complete inhibition of the bacterial growth and reproduction; ⁷Melphalan - reference compound; ⁸Isoniazid - reference compound and ⁹EMB-2HCl (ethambutol dihydrochloride) - reference compound.

**Antimycobacterial activity.** The in vitro antimycobacterial activity of all compounds against *Mycobacterium tuberculosis* H37Rv reference strain was evaluated using the proportional method of Canetti and the resazurin microtiter assay. Ethambutol - EMB-2HCl (ethambutol dihydrochloride) and isoniazid were used as controls. The MIC is defined as the lowest concentration effecting the 100 % reduction in fluorescence, relative to controls. The data for the compounds 5 and 7 are shown in Table 1. The tested compounds exhibited significant antimycobacterial activity against the chosen strain, whereby the MIC values were within the nanomolar range, lower than those of ethambutol and INH.

**CONCLUSION**

New thiazolidine-2,4-dione and hydantoin derivatives were synthesized and their structures were elucidated on the basis of FTIR, ¹H NMR, ¹³C NMR, 2D spectra (COSY, HMQC, HMBC) and HRMS data. The aldol product 5 was exclusively obtained in (Z)-configuration. The compounds 5 and 7, were tested for cytotoxic activity with MTT-dye reduction assay against leukemia-derived HL-60 cells, REH, K-562, and urinary bladder...
carcinoma cells (EJ). The tested compounds displayed promising micromolar antiproliferative activity. The most potent compound was 2H-chromene derivative 5 with IC$_{50}$ values ranging from 13.1 - 0.98 µM. Also, the tested compounds 5 and 7 were found highly potent against the M. tuberculosis H37Rv, demonstrating a nanomolar activity (MICs ranging from 0.27 to 0.71 µM). The obtained results could be useful for the design and synthesis of new substituted 2,4-thiazolidindione with superior antiproliferative potencies as potential anticancer agents. Taken together our data give the reason to consider 2,4-imidazolinone derivative 5 and hydantoin derivative 7 promising new leads for further exploration as potential antimycobacterial agents.

REFERENCES


СИНТЕЗ, ИН ВИТРО АНТИПРОЛИФЕРАТИВНА И АНТИМИКОБАКТЕРИАЛНА АКТИВНОСТ НА ТИАЗОЛИДИН-2,4-ДИОН И ХИДАНТОИНОВИ ПРОИЗВОДНИ

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(Резюме)

Синтезирани са нови 2Н-хроменови производни, съдържащи тиазолидин-2,4-дионов и хидантоинов фрагмент и структурата им е потвърдена чрез 1Н NMR, 13С NMR, 2D NMR, FTIR спектрални методи и HR-ESI-MS. Съединенията са изследвани ин витро за цитотоксичната им активност срещу четири човешки туморни клетъчни линии - HL-60 (остра промиелоцитна левкемия), REH (лимфоидна левкемия), K-562 (хронична миелоидна левкемия) и EJ (карцином на пикочния мехур). 2Н-Хромен съдържащият тиазолидин-2,4-дион 5 e мого активен срещу три ракови клетъчни линии, с IC50 от порядъка на 13.1-39.6 µM и показва най-изразена антипrolиферативна активност срещу лимфоидна левкемия (клетъчна линия REH) със стойност на IC50 = 13.1 µM. Хидантоин съдържащото 2Н-хроменово производно 7 e високо най-ефективно срещу хронична миелоидна левкемия K-562 със стойност на IC50 = 83.7 µM. Съединенията 5 и 7 демонстрират също и значителна антимикобактериална активност срещу Mycobacterium tuberculosis H37Rv с минимална инхибираща концентрация (MIC) в диапазона от 0.29 и 0.36 µM, съответно.