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SYNTHESIS OF NEW 5-(CHROMENE-3-YL)METHYLENE-2,4-THIAZOLIDINEDIONES

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ABSTRACT. With the aim of developing new biologically active compounds, a series of new *N*-substituted 5-(chromene-3-yl)methylene-2,4- thiazolidinediones **3**-**12** has been synthesized. First step was the condensation of different chromone-3-carbaldehydes with 2,4-thiazolidinedione, followed by the reaction with various α-bromoalkylarylketones. The structures of all new compounds were confirmed by elemental analysis, mass spectra and ^{1}H NMR studies.

Keywords: *chromone; thiazolidinedione; α-bromoalkylarylketones*

INTRODUCTION

Microbial resistance represents, for more than decades, a real threat for the efficiency of current drug therapy [1-3]. For the patients at risk, this may involve prolonging the disease or even death. The main reasons for the increasing microbial resistance are: inappropriate use of antibiotics and the lack of compliance from patients, inappropriate prescribing [4], increasing number of immunocompromised patients, excessive use of antibiotics in the veterinary practice and decreased financial investments of big pharmaceutical companies in the research activities for discovering new potent antimicrobial drug. In 2014, WHO signalized the resistance of 9 bacterial strains to classic treatment. In the case of fungal infections, the increased resistance to azole drugs and the emergence of strains resistant to echinocandins, the newest class of antifungal agents, was reported [5].

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Nowadays, efforts are being made for the control of microbial resistance phenomenon, limiting the global spread and its effects. The research in this area is orientated towards the discovery of a new potent drug, with an original chemical structure and, why not, an original mechanism of action.

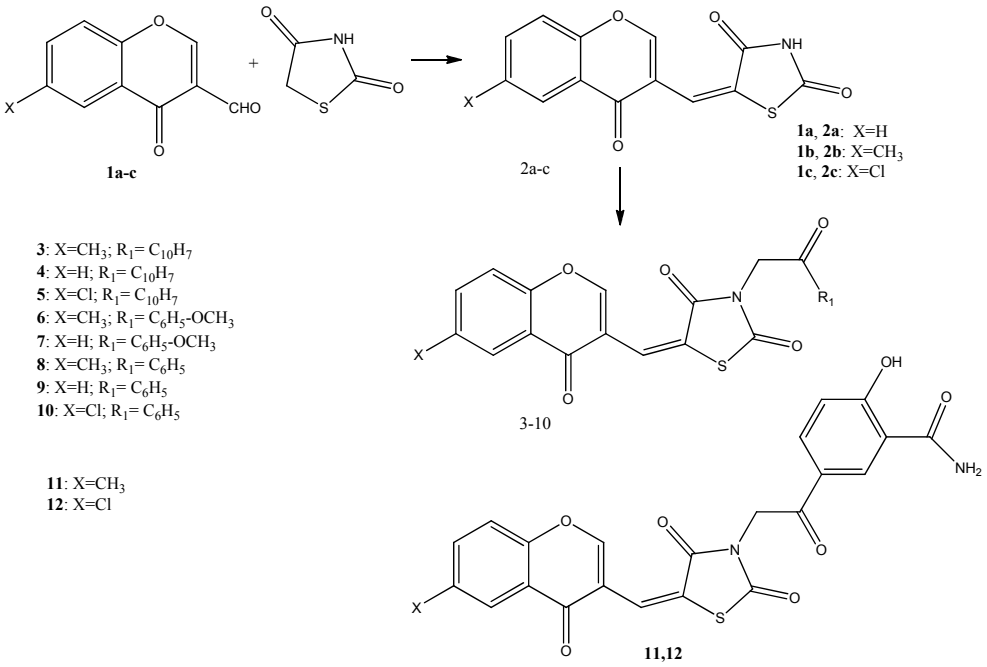
From the big family of heterocyclic compounds, the five-membered rings, containing two heteroatoms, receive special attention, due to their large spectrum of biological activities. A considerable amount of work has been done on the synthesis of thiazolidinedione derivatives as potent antibacterial and antifungal agents [6-10]. Chromones belong to the important class of oxygen-containing heterocyclic compounds and they are part of the flavonoid family. These compounds are widespread in nature and exhibit a wide range of pharmacological activity like antibacterial, antifungal [11-14], antitumor, antioxidant, anti-HIV, anti-inflammatory. Therefore, the vast range of biological effects associated with this scaffold has resulted in the chromone ring system being considered as a privileged structure in medicinal chemistry.

The association of two or more pharmacophores inside the same molecule may be associated with the increase of the biological effects. As a continuation of our work [15] and considering the facts presented above, we describe here, in this paper, the chemical synthesis of a new series of *N*-substituted 5-(chromene-3-yl)methylene-2,4-thiazolidinediones, which gather two important scaffolds in medicinal chemistry.

RESULTS AND DISCUSSION

Synthesis of new *N*-substituted 5-chromenyl-thiazolidinediones had two steps. First consisted in Knoevenagel condensation of 2,4-thiazolidinedione with 3-formyl-chromones **1a-c**, in acetic acid and in the presence of anhydrous sodium acetate (**Scheme 1**). Synthesis of compounds **2a** and **2b** was done according to literature data [16], and compound **2c** was obtained in our laboratory, following the same procedure [15]. The new derivatives were treated with various α-bromoalkylarylketones, in the presence of anhydrous potassium hydroxide and dimethylformamide (DMF), in order to obtain, in good yields, the new *N*-substituted molecules **3-12**.

The compounds were isolated, the melting points were registered and the purity was confirmed by thin layer chromatography (TLC). All new molecules were characterized by elemental analysis and spectroscopic data (NMR, MS), which were consistent with the assigned structures.



Scheme 1. Synthesis of new *N*-substituted chromenyl-thiazolidinediones
i: anhydrous sodium acetate/acetic acid, 3h reflux; ii: α-bromoalkylarylketones, anhydrous potassium hydroxide, DMF, 30 minutes, stirring, room temperature

The ^{1}H NMR spectra showed characteristic singlets due to –CH= proton bound in position 5 of thiazolidinedione system, at δ 7.74–7.80 ppm, demonstrating the synthesis of 5-chromenyl-thiazolidinediones.

The disappearance, in the spectra, of the signal due to the H from -NH- in thiazolidinedione heterocycle and the appearance of signals specific for the phenyl protons, put in evidence the *N*-substitution and thus, the synthesis of the new derivatives.

CONCLUSIONS

The present work describes the synthesis of ten new *N*-substituted chromenyl-thiazolidinediones **3**-**12**. Compounds **2a** and **2b** were reproduced after the techniques presented in the literature and 5-chromenyl-thiazolidinedione **2c** was previously obtained in our research laboratory, using the same procedure. The structures of all new synthesized molecules were fully confirmed by physical data, elemental analyses and ^{1}H NMR spectroscopy in solution.

EXPERIMENTAL SECTION

General

Solvents were obtained from commercial sources. Analytical thin layer chromatography was carried out on precoated Silica Gel $60F_{254}$ sheets using UV absorption for visualization. The melting points were taken with MPM-H1 Schorpp melting point meter, and are uncorrected. The ^{1}H NMR spectra were recorded at room temperature on a Bruker Avance NMR spectrometer operating at 500 MHz and were in accord with the assigned structures. Chemical shift values were reported relative to tetramethylsilane (TMS) as internal standard. The samples were prepared by dissolving the synthesized powder of the compounds in DMSO-d_6 (δ_H= 2.51 ppm) as solvent. Mass spectra were recorded by Agilent 1100, type SL spectrometer (positive ionization) and with a Varian MAT CH-5 spectrometer (70 eV). Elemental analysis was registered with a Vario El CHNS instrument.

Synthesis

General procedure

*Synthesis of 5-chromenyl-2,4-thiazolidinedione (**2a** and **2b**)*

1 mmol of 4-oxo-4*H*-chromene-3-carbaldehyde **1a** or 6-methyl-4-oxo-4*H*-chromene-3-carbaldehyde **1b** was refluxed for 3 h with 1 mmol (0.117 g) of 1,3-thiazolidine-2,4-dione and 4 mmol (0.328 g) of anhydrous sodium acetate in 5 ml of acetic acid, according to the literature data [16]. The reaction mixture was cooled, and the crude product was filtered under reduced pressure, washed with water on the filter and purified by recrystallization from ethanol. Compound **2c** was obtained following the same procedure, starting from 6-chloro-4-oxo-4*H*-chromene-3-carbaldehyde **1c** [15].

*Synthesis of N-substituted 5-chromenyl-2,4-thiazolidinedione (**3-12**)*

For synthesis, 1 mmol of 5-chromenyl-2,4-thiazolidinedione **2a-c** was stirred for 30 minutes, at room temperature, with 1.1 mmol (0.062 g) of anhydrous potassium hydroxide, in 6 ml of DMF. After the potassium salt was formed, 1.1 mmol of α-bromoalkylarylketones were added. The crude product was filtered under reduced pressure, washed with water on the filter and purified by recrystallization from ethanol.

5-((6-methyl-4-oxo-4H-chromen-3-yl)methylene)-3-(2-(naphtalen-2-yl)-2oxoethyl) thiazolidine-2,4-dione (**3**)

Yield 95 %. White powder, mp: 251 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 2.46 (s, 3H, -CH_3); 5.45 (s, 2H, -CH_2-); 7.66 (d, 1H, C_8-chromone-H); 7.68 (dd, 1H, C_7-chromone-H); 7.68-7.74 (m, 1H, naphtyl); 7.70 (dd, 1H, naphtyl); 7.75 (d, 1H, naphtyl); 7.78 (s, 1H, C=CH); 7.95 (s, 1H, C_5-chromone-H); 8.05 (d, 1H, naphtyl); 8.09 (d, 1H, naphtyl); 8.17 (d, 1H, naphtyl); 8.90 (s, 1H, naphtyl); 8.97 (s, 1H, C_2-chromone-H). Anal. Calcd. (%) for $C_{26}H_{17}NO_5S$ (455.48): C, 68.56; H, 3.76; N, 3.08; S, 7.04. Found: C, 68.55; H, 3.76; N, 3.08; S, 7.04. MS (EI, 70 eV): *m/z* 456.5 [M+1].

3-(2-(naphtalen-2-yl)-2-oxoethyl)-5-((4-oxo-4H-chromen-3-yl)methylene) thiazolidine-2,4-dione (**4**)

Yield 85 %. White powder, mp: 264 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 5.41 (s, 2H, -CH_2-); 7.57 (d, 1H, C_6-chromone-H); 7.67 (d, 1H, C_8-chromone-H); 7.68 (dd, 1H, C_7-chromone-H); 7.69-7.73 (m, 1H, naphtyl); 7.70 (dd, 1H, naphtyl); 7.76 (d, 1H, naphtyl); 7.78 (s, 1H, C=CH); 7.94 (s, 1H, C_5-chromone-H); 8.04 (d, 1H, naphtyl); 8.09 (d, 1H, naphtyl); 8.16 (d, 1H, naphtyl); 8.91 (s, 1H, naphtyl); 8.96 (s, 1H, C_2-chromone-H). Anal. Calcd. (%) for $C_{25}H_{15}NO_5S$ (441.46): C, 68.02; H, 3.42; N, 3.17; S, 7.26. Found: C, 68.03; H, 3.42; N, 3.15; S, 7.27. MS (EI, 70 eV): *m/z* 442.5 [M+1].

5-((6-chloro-4-oxo-4H-chromen-3-yl)methylene)-3-(2-(naphtalen-2-yl)-2oxoethyl) thiazolidine-2,4-dione (**5**)

Yield 83 %. Yellow powder, mp: 252 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): 5.42 (s, 2H, -CH_2-); 7.61 (d, 1H, C_8-chromone-H); 7.67 (dd, 1H, C_7-chromone-H); 7.68-7.72 (m, 1H, naphtyl); 7.74 (dd, 1H, naphtyl); 7.76 (d, 1H, naphtyl); 7.80 (s, 1H, C=CH); 7.94 (s, 1H, C_5-chromone-H); 8.04 (d, 1H, naphtyl); 8.08 (d, 1H, naphtyl); 8.18 (d, 1H, naphtyl); 8.92 (s, 1H, naphtyl); 8.98 (s, 1H, C_2-chromone-H). Anal. Calcd. (%) for $C_{25}H_{14}ClNO_5S$ (475.9): C, 63.09; H, 2.97; N, 2.94; S, 6.74. Found: C, 63.10; H, 2.97; N, 2.93; S, 6.75. MS (EI, 70 eV): *m/z* 477 [M+1].

3-(2-(4-methoxyphenyl)-2-oxoethyl)-5-((6-methyl-4-oxo-4H-chromen-3-yl) methylene) thiazolidine-2,4-dione (**6**)

Yield 76 %. Yellow powder, mp: 238 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 3.03 (s, 3H, -CH_3); 3.06 (s, 3H, -CH_3); 5.23 (s, 2H, -CH_2-); 7.12 (d, 2H, phenyl); 7.65 (d, 1H, C_8-chromone-H); 7.71 (dd, 1H, C_7-chromone-H); 7.75 (s, 1H, C=CH); 7.94 (s, 1H, C_5-Chromone-H); 8.06 (d, 2H, phenyl); 8.95 (s, 1H, C_2-chromone-H). Anal. Calcd. (%) for $C_{23}H_{17}NO_6S$ (435.45): C, 63.44; H, 3.94; N, 3.22; S, 7.36. Found: C, 63.43; H, 3.93; N, 3.21; S, 7.37. MS (EI, 70 eV): *m/z* 436.5 [M+1].

3-(2-(4-methoxyphenyl)-2-oxoethyl)-5-((4-oxo-4H-chromen-3-yl) methylene)thiazolidine-2,4-dione (**7**)

Yield 99 %. White powder, mp: 254 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 2.46 (s, 3H, -CH_3); 5.20 (s, 2H, -CH_2-); 7.14 (d, 2H, phenyl); 7.56 (d, 1H, C_6-chromone-H); 7.62 (d, 1H, C_8-chromone-H); 7.70 (dd, 1H, C_7-chromone-H); 7.74 (s, 1H, C=CH); 7.98 (s, 1H, C_5-Chromone-H); 8.04 (d, 2H, phenyl); 8.98 (s, 1H, C_2-chromone-H). Anal. Calcd. (%) for $C_{22}H_{15}NO_6S$ (421.42): C, 62.70; H, 3.59; N, 3.32; S, 7.61. Found: C, 62.71; H, 3.59; N, 3.32; S, 7.62. MS (EI, 70 eV): *m/z* 422.5 [M+1].

5-((6-methyl-4-oxo-4H-chromen-3-yl)methylene)-3-(2-oxo-2-phenylethyl)thiazolidine-2,4-dione (**8**)

Yield 78**%**. Light brown powder, mp: 228 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 2.45 (s, 3H, -CH_3); 5.30 (s, 2H, -CH_2-); 7.61 (t, 2H, phenyl); 7.65 (d, 1H, C_8-chromone-H); 7.70 (dd, 1H, C_7-chromone-H); 7.75 (t, 1H, phenyl); 7.76 (s, 1H, C=CH); 7.94 (s, 1H, C_5-Chromone-H); 8.09 (d, 2H, phenyl); 8.95 (s, 1H, C_2-chromone-H). Anal. Calcd. (%) for $C_{22}H_{15}NO_5S$ (405.42): C, 65.18; H, 3.73; N, 3.45; S, 7.91. Found: C, 65.19; H, 3.72; N, 3.45; S, 7.92. MS (EI, 70 eV): *m/z* 406.5 [M+1]].

3-(2-oxo-2-phenylethyl)-5-((4-oxo-4H-chromen-3-yl)methylene) thiazolidine-2,4-dione (**9**)

Yield 93 %. Light yellow powder, mp: 252 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 5.32 (s, 2H, -CH_2-); 7.58 (d, 1H, C_6-chromone-H); 7.63 (t, 2H, phenyl); 7.67 (d, 1H, C_8-chromone-H); 7.70 (dd, 1H, C_7-chromone-H); 7.72 (t, 1H, phenyl); 7.76 (s, 1H, C=CH); 7.91 (s, 1H, C_5-Chromone-H); 8.08 (d, 2H, phenyl); 8.90 (s, 1H, C_2-chromone-H). Anal. Calcd. (%) for $C_{21}H_{13}NO_5S$ (391.40): C, 64.44; H, 3.35; N, 3.58; S, 8.19. Found: C, 64.45; H, 3.35; N, 3.58; S, 8.20. MS (EI, 70 eV): *m/z* 392.5 [M+1].

5-((6-chloro-4-oxo-4H-chromen-3-yl)methylene)-3-(2-oxo-2-phenylethyl)thiazolidine-2,4-dione (**10**)

Yield 84 %. Yellow powder, mp: 243 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 5.28 (s, 2H, -CH_2-); 7.64 (t, 2H, phenyl); 7.66 (d, 1H, C_8-chromone-H); 7.72 (dd, 1H, C_7-chromone-H); 7.75 (t, 1H, phenyl); 7.77 (s, 1H, C=CH); 7.92 (s, 1H, C_5-Chromone-H); 8.10 (d, 2H, phenyl); 8.90 (s, 1H, C_2-chromone-H). Anal. Calcd. (%) for $C_{21}H_{12}ClNO_5S$ (425.84): C, 59.23; H, 2.84; N, 3.29; S, 7.53. Found: C, 59.22; H, 2.83; N, 3.28; S, 7.54. MS (EI, 70 eV): *m/z* 427 [M+1].

2-hydroxy-5-(2-(5-((6-methyl-4-oxo-4H-chromen-3-yl)methylene)-2,4-dioxothiazolidin-3-yl)acetyl)benzamide (**11**)

Yield 30 %. Light brown powder, mp: 303 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 2.51 (s, 3H, -CH_3); 5.29 (s, 2H, -CH_2-); 7.08 (d, 1H, phenyl); 7.42 (d, 1H, phenyl); 7.66 (d, 1H, C_8-chromone-H); 7.72 (dd, 1H, C_7-chromone-H); 7.77 (s, 1H, C=CH); 7.95 (s, 1H, C_5-Chromone-H); 7.98 (br, 1H, -CO-NH_2); 8.12 (dd, 1H, phenyl); 8.43 (br, 1H, -CO-NH_2); 8.96 (s, 1H, C_2-chromone-H); 13.97 (s, 1H, Ar-OH). Anal. Calcd. (%) for $C_{23}H_{16}N_2O_7S$ (464.45): C, 59.48; H, 3.47; N, 6.03; S, 6.90. Found: C, 59.49; H, 3.47; N, 6.01; S, 6.90. MS (EI, 70 eV): *m/z* 465.5 [M+1].

5-(2-(5-((6-chloro-4-oxo-4H-chromen-3-yl)methylene)-2,4-dioxothiazolidin-3-yl) acetyl)-2-hydroxybenzamide (**12**)

Yield 30 %. Light yellow powder, mp: 303 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 5.28 (s, 2H, -CH_2-); 7.09 (d, 1H, phenyl); 7.44 (d, 1H, phenyl); 7.66 (d, 1H, C_8-chromone-H); 7.71 (dd, 1H, C_7-chromone-H); 7.78 (s, 1H, C=CH); 7.97 (s, 1H, C_5-Chromone-H); 7.98 (br, 1H, -CO-NH_2); 8.10 (dd, 1H, phenyl); 8.42 (br, 1H, -CO-NH_2); 8.94 (s, 1H, C_2-chromone-H); 13.92 (s, 1H, Ar-OH). Anal. Calcd. (%) for $C_{22}H_{13}ClN_2O_7S$ (484.87): C, 54.50; H, 2.70; N, 5.78; S, 6.61. Found: C, 54.49; H, 2.70; N, 5.79; S, 6.60. MS (EI, 70 eV): *m/z* 486 [M+1].

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