

Communication

Synthesis of a New [3-(4-Chlorophenyl)-4-oxo-1,3-thiazolidin-5-ylidene]acetic Acid Derivative

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Abstract: The new methyl [3-(4-chlorophenyl)-2-[(2,4-dichloro-1,3-thiazol-5-yl)methylidene]hydrazinylidene]-4-oxo-1,3-thiazolidin-5-ylidene]acetate was synthesized from 4-(4-chlorophenyl)-1-(2,4-dichloro-1,3-thiazol-5-yl)methylidene-3-thiosemicarbazide using dimethyl acetylenedicarboxylate as thia-Michael reaction acceptor. New compounds (**3** and **4**) were characterized by IR, ¹H and ¹³C NMR spectroscopy methods.

Keywords: thiazolidin-4-one; Michael addition; anti-*T. gondii* activity

1. Introduction

Toxoplasmosis is a common parasitic infectious disease that occurs all over the world. Toxoplasmosis is caused by the protozoan *Toxoplasma gondii*, whose ultimate host is Felidae. Approximately 30% of people have positive antibodies indicating toxoplasmosis [1]. The basic danger of the disease is the possibility of congenital infections during pregnancy and the reactivation of the disease in immunocompromised persons.

Over the last decade, the scientific value of thiazolidin-4-one derivatives has increased due to their wide spectrum of biological activities, including antidiabetic, anticancer, antibacterial, antifungal, anti-inflammatory, etc. The activity and mechanisms of action of thiazolidin-4-ones are described in numerous reviews [2–7]. It is also worth paying attention to the anti-*T. gondii* activity of thiazolidin-4-ones [8–12].

In addition, the currently used drugs are not 100% effective for the treatment of toxoplasmosis, and this has prompted us to look for new synthetic compounds that could be used to combat this common parasite in the future.

In our previous research [12], we identified (4-oxothiazolidin-5-yl/ylidene)acetic acid derivatives with antiparasitic activity against *T. gondii* (Figure 1). The highlighted fragments (green and orange color) in Figure 1 are favorable for anti-*T. gondii* activity. Based on previous studies, we designed a compound which contains both highlighted fragments.

In this communication, we describe the synthesis of the previously unknown methyl [3-(4-chlorophenyl)-2-[(2,4-dichloro-1,3-thiazol-5-yl)methylidene]hydrazinylidene]-4-oxo-1,3-thiazolidin-5-ylidene]acetate, which has potential as an anti-*T. gondii* agent.

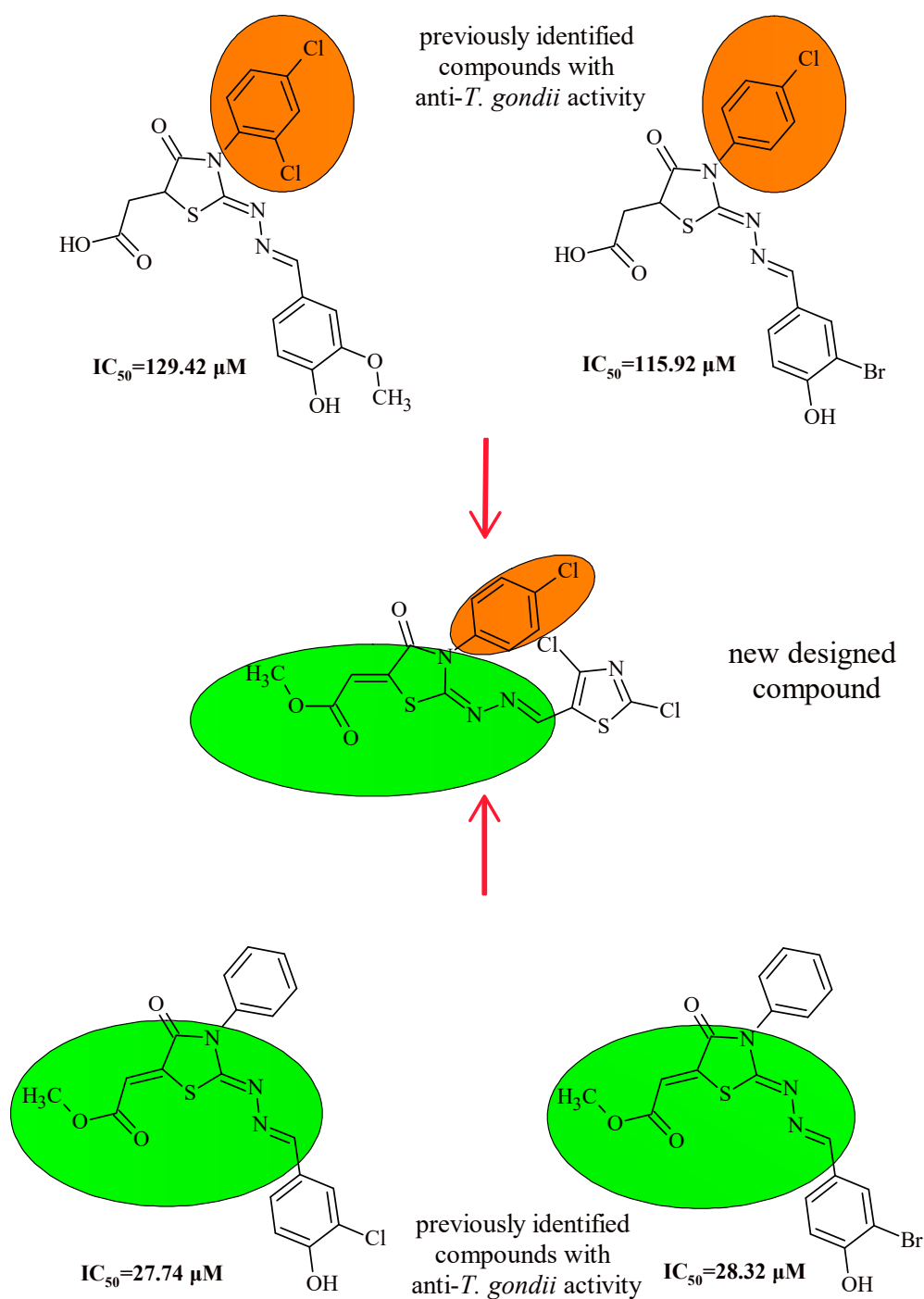
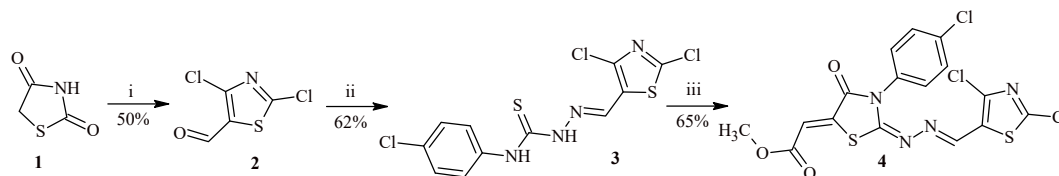


Figure 1. (4-Oxothiazolidin-5-yl/ylidene)acetic acid derivatives with anti-*T. gondii* activity and new designed compound.

2. Results and Discussion

The targeted compound was synthesized by three-step synthesis starting from thiazolidine-2,4-dione (TZD). TZD was converted into 2,4-dichloro-1,3-thiazol-5-carbaldehyde via a Vilsmeier–Haack reaction in accordance with the literature [13]. In the next step, 2,4-dichloro-1,3-thiazol-5-carbaldehyde (2) was condensed with 4-(4-chlorophenyl)-3-thiosemicarbazide to give the thiosemicarbazone (3). In the last step of synthesis, the targeted compound was obtained from 4-(4-chlorophenyl)-1-(2,4-dichloro-1,3-thiazol-5-yl)methylidene-3-thiosemicarbazide (3) and dimethyl acetylenedicarboxylate

by thia-Michael addition of the sulfur atom to the triple bond and then cyclization to give the (4-oxothiazolidin-5-ylidene)acetic acid derivative **4** (Scheme 1), which illustrates that precursor **3** is also useful for this type of reaction, if other compounds (maleic anhydride, maleimide derivatives etc.) are used as acceptors in the thia-Michael addition.



Scheme 1. Synthetic route for compound **4**. *Reagents and conditions:* (i) POCl₃, DMF stirred for 1 h at rt, heat for 1 h at 80–90 °C, brought to boil and heated for another 4 h; (ii) 4-(4-chlorophenyl)-3-thiosemicarbazide, EtOH, heated under reflux for 3 h; and (iii) dimethyl acetylenedicarboxylate, MeOH, heated under reflux for 30 min.

The structures of compounds **3** and **4** were supported by IR, ¹H, and ¹³C NMR spectroscopy methods (see Supplementary Materials). The ¹H NMR spectra exhibit the characteristic signals for *para*-substituted phenyl ring as two doublets in the range 7.44 to 7.76 ppm with spin–spin coupling $J = 8.7$ Hz. The signals derived from the proton of a CH=N group were observed at 8.29 ppm and 8.30 ppm for compounds **3** and **4**, respectively. The characteristic proton signal of methylenidene group (CH=) of compound **4** was observed as singlet at 6.94 ppm. All remaining signals arising from other parts of the molecule were present. Similarly, ¹³C NMR confirmed present of all carbon atoms in molecule (details were presented in the experimental part).

3. Materials and Methods

3.1. General

All commercial reagents and solvents were purchased from either Alfa Aesar (Lancaster, UK) or Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. The melting points were determined by using Gallenkamp MPD 350.BM 3.5 apparatus Sanyo (Moriguchi, Japan) and are uncorrected. The purity of the compound was checked by TLC on plates with silica gel Si 60F₂₅₄, produced by Merck Co. (Darmstadt, Germany). The ¹H NMR and ¹³C NMR spectra were recorded by a Bruker Avance 300 MHz instrument (Bruker Corporation, Billerica, MA, USA) using DMSO-*d*₆ as solvent and TMS as an internal standard. Chemical shifts were expressed as δ (ppm). IR spectrum was recorded by Nicolet 6700 spectrometer (Thermo Scientific, Philadelphia, PA, USA). Elemental analysis was performed by AMZ 851 CHX analyzer (PG, Gdańsk, Poland) and the results were within $\pm 0.4\%$ of the theoretical value.

3.2. 4-(4-Chlorophenyl)-1-(2,4-dichloro-1,3-thiazol-5-yl)methylidene-3-thiosemicarbazide (**3**)

To the 2,4-dichloro-1,3-thiazole-5-carbaldehyde (**2**) (1.27 g, 7 mmol) and 4-(4-chlorophenyl)-3-thiosemicarbazide (1.41 g, 7 mmol), anhydrous ethanol (20 mL) and glacial acetic acid (79 mg, 5 drops) were added. The reaction mixture was heated under reflux for 3 h. After cooling, the precipitate was filtered off. After drying, precipitate was crystallized from acetic acid.

Yield 1.59 g (62%), orange powder, mp = 198–200 °C. IR ν (cm⁻¹): 3294 (NH), 3054 (CH_{ar}), 1589, 1549 (C=N). ¹H NMR (300 MHz, DMSO-*d*₆) δ : 7.44 (2H, d, $J = 8.7$ Hz, Ar H); 7.56 (2H, d, $J = 8.7$ Hz, Ar H); 8.29 (1H, s, CH=N); 10.12 (1H, s, NHCSNH); 12.16 (1H, s, NHCSNH). ¹³C NMR (75 MHz, DMSO-*d*₆) δ : 128.1 (CH_{ar}), 128.5 (CH_{ar}), 130.1 (C_{ar}), 130.5 (C_{ar}), 133.3 (CH=N), 136.9 (N=CH-C), 138.3 (=C(Cl)-N), 152.6 (S-C(Cl)=N), 176.6 (C=S). Anal. calc. for C₁₁H₇Cl₃N₄S₂ (365.689) (%): C 36.13; H 1.93; N 15.32. Found: C 36.07; H 1.89; N 15.27.

3.3. Methyl [3-(4-chlorophenyl)-2-[(2,4-dichloro-1,3-thiazol-5-yl)methylidene]hydrazinylidene]-4-oxo-1,3-thiazolidin-5-ylidene]acetate (**4**)

To the thiosemicarbazone **3** (0.73 g, 2 mmol) dimethyl acetylenedicarboxylate (0.25 mL, 2 mmol) and methanol (15 mL) were added. The reaction mixture was heated under reflux for 30 min. After cooling, the precipitate was filtered off. After drying, precipitate was crystallized from a mixture of solvents DMF/acetic acid in volume ratio (1/1).

Yield 0.62 g (65%), yellow powder, mp = 248–250 °C. IR ν (cm⁻¹): 3056 (CH_{ar}), 1730 (C=O ester), 1690 (C=O thiazolidine), 1587, 1550 (C=N); ¹H NMR (300 MHz, DMSO-*d*₆) δ : 3.85 (3H, s, OCH₃); 6.94 (1H, s, H₃COOC-CH=); 7.64 (2H, d, *J* = 8.7 Hz, Ar H); 7.76 (2H, d, *J* = 8.7 Hz, Ar H); 8.30 (1H, s, CH=N). ¹³C NMR (75 MHz, DMSO-*d*₆) δ : 53.3 (OCH₃); 117.1 (CH=C); 122.3 (CH=C); 130.3 (CH_{ar}); 131.1 (CH_{ar}); 133.7 (C_{ar}); 135.2 (N=CH-C); 140.8 (=C(Cl)-N); 141.3 (C_{ar}); 145.9 (CH=N); 158.5 (S-C(Cl)=N); 164.3 (C=N); 164.6 (C=O thiazolidine); 166.4 (C=O ester). Anal. calc. for C₁₆H₉Cl₃N₄O₃S₂ (475.757) (%): C 40.39; H 1.91; N 11.78. Found: C 40.26; H 1.90; N 11.77.

4. Conclusions

The result of our current research is the new (4-oxothiazolidin-5-ylidene)acetic acid derivative. It has been synthesized in good yield from 4-(4-chlorophenyl)-1-(2,4-dichloro-1,3-thiazol-5-yl)methylidene-3-thiosemicarbazide by thia-Michael reaction with next cyclization. This compound can be of interest to the medicinal science branch due to its potential as an anti-*T. gondii* agent.

Supplementary Materials: The following are available online, Figures S1–S6: IR, ¹H, and ¹³C NMR spectra for compounds **3** and **4**.

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