

Microwave-assisted Synthesis of New 1,3-thiazolidin-4-ones and Evaluation of Their Anticancer Efficacy

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Abstract

An efficient method for the synthesis of thiazolidinones from the microwave-assisted, three-component mixture of an aromatic aldehyde, a 2-amino-4*H*-benzothiopyrano[4,3-*d*]thiazole and meraptoacetic acid is described. The transformation of the amino group of 2-amino-4*H*-[1]benzothiopyrano[4,3-*d*]thiazoles into a thiazolidinone ring has not been reported to date. *In vitro* their anticancer activity was evaluated by MTT method. The results of bioactivities evaluation showed the compound 4 exhibited the best anticancer activity and its IC₅₀ was 5.76 μM, 6.19 μM, 6.67 μM against gastric cancer cells (SGC-7901), cervical cancer cells (Hela) and lung cancer cells (A-549), respectively.

Keywords: 1,3-thiazolidin-4-ones, 4*H*-thiochromeno[4,3-*d*]thiazol-2-amines, Anticancer activity, DCC, Microwave-assisted synthesis

1. Introduction

Thiazoles are one of the most intensively investigated classes of aromatic five membered heterocycles. Thiazole derivatives find a variety of applications ranging from anti-fungal and anti-bacterial through to CNS regulators of commercially successful diuretics. All these facts were driving force to develop novel thiazole derivatives with wide structural variation.

Thiazolidin-4-ones have played an important role in medicinal chemistry. Moreover they have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activity, such as anti-HIV (Ravindra, K.R., 2007; Murugesan, V., 2009; Balzarini, J., 2007; Küçüküzümlü, G., 2006), anti-mycobacterial (Aridoss, G., 2009), anti-proliferative (Ottana, R., 2005), anti-microbial (Mujeebur, R.V.P., 2005; Vicini, P., 2008; Vicini, P., 2006), anti-inflammatory (Ottana, R., 2005), anti-cancer (Chen, Hua,

2008), anti-fungal (Dandia, A., 2006). Studies revealed that a 2-(thiazolyl)substituent at N-3 of a 1,3-thiazolidin-4-one displayed anti-microbial and anti-HIV activity (Ravindra, K.R., 2007). Thiochromanones also had been reported to possess important biological activities. In this paper, thiochromanones (1) as the starting material were transformed into 4*H*-thiochromeno[4,3-*d*]thiazol-2-amines (2) and providing amino parts. The transformation of the amino group of 2-amino-4*H*-[1]benzothiopyrano[4,3-*d*]thiazoles into a thiazolidinone ring has not been reported to date. It was worthy to explore this unusual heterocyclic system and investigate any potential anticancer activity.

2. Experimental

2.1 Chemistry

MW experiments were carried out in Microwave synthesizer. Melting points of all compounds synthesized were determined with a SGW X-4 melting point apparatus. The ¹H NMR spectra were recorded in CDCl₃ at 600 MHz with a AVANCE 600 spectrometer (internal standard TMS, $\delta=0.0$ ppm). IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). The MS spectra were measured on LC-MSD Trap XCT spectrometer. Elemental analysis was performed on a Carlo Erba-1106 instrument and the results were in acceptable range. All materials were commercially available and used as received unless otherwise noted. Substituted 4*H*-thiochromeno-[4,3-*d*]thiazol-2-amines were prepared according to method reported (Zhan Fuxun, 2009).

2.2 Preparation of compounds 3

Substituted 4*H*-thiochromeno[4,3-*d*]thiazol-2-amine (5.00 mmol), aromatic aldehyde (5.00 mmol) and mercaptoacetic acid (10.00 mmol) were added in microwave reaction tube (10 mL), added toluene (4 mL) dissolved the mixture, then added DCC (Dicyclohexylcarbodiimide, 10.00 mmol). The reaction tube was irradiated at 140 °C for 10 min. Upon completion, cooled to room temperature, the solids were filtered and added CHCl₃ (20 mL) to the filtrate, sequentially washed with saturated NaHCO₃, H₂O, brine and then dried over anhydrous MgSO₄. Solvent was removed under reduced pressure to provide a crude product which was purified by column chromatography (silica gel, ethyl acetate: petroleum=1:40-1:10(v/v)) to afford pure 3.

2.2.1 3-(8-Chloro-4*H*-thiochromeno[4,3-*d*]thiazol-2-yl)-2-(4-methoxyphenyl)thiazolidin-4-one (3a)

Yield 50% of red brown solid, m.p. 123-125 °C, UV-vis (MeOH) $\lambda_{\max}$: 238 nm; IR (KBr) ν : 3010, 1689, 1610, 1600, 1089, 1471, 877, 837 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ : 3.78 (s, 3H, OCH₃), 3.87 (d, J = 16.43 Hz, 1H, COCH₂S), 4.03 (d, J = 15.08 Hz, 1H, COCH₂S), 4.08-4.17 (m, 2H, SCH₂), 6.63 (s, 1H, NCHS), 6.88 (d, J = 8.74 Hz, 2H, Ar-H), 7.08 (dd, J = 8.31, 2.33 Hz, 1H, Ar-H), 7.16 (d, J = 8.30 Hz, 1H, Ar-H), 7.34 (d, J = 8.75 Hz, 2H, Ar-H), 7.60 (d, J = 2.31 Hz, 1H, Ar-H); MS (APCI) m/z : 446.8 (M+H)⁺, 448.8 (M+2+H)⁺. Anal. Calcd for C₂₀H₁₅ClN₂O₂S₃: C 53.74, H 3.38, N 6.88, S 21.57; Found C 53.69, H 3.33, N 6.83, S 21.53.

2.2.2 3-(8-Chloro-4*H*-thiochromeno[4,3-*d*]thiazol-2-yl)-2-(furan-2-yl)thiazolidin-4-one (3b)

Yield 60% of pale brown solid, m.p. 177-179 °C, UV-vis (MeOH) $\lambda_{\max}$: 238 nm; IR (KBr) ν : 1689, 1620, 1588, 1506, 1488, 1458 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ : 3.77 (d, J = 16.06 Hz, 1H, COCH₂S), 4.13-4.06 (m, 2H, SCH₂), 4.28 (d, J = 16.13 Hz, 1H, COCH₂S), 6.33 (dd, J = 3.28, 1.84 Hz, 1H, furan-H), 6.43 (d, J = 3.25 Hz, 1H, furan-H), 6.74 (s, 1H, NCHS), 7.11 (dd, J = 8.32, 2.39 Hz, 1H, Ar-H), 7.20 (d, J = 8.31 Hz, 1H, Ar-H), 7.36 (d, J = 1.08 Hz, 1H, furan-H), 7.76 (d, J = 2.32 Hz, 1H, Ar-H); MS (APCI) m/z : 406.5 (M+H)⁺, 408.5 (M+2+H)⁺. Anal. Calcd for C₁₇H₁₁ClN₂O₂S₃: C 50.18, H 2.72, N 6.88, S 23.64; Found C 50.14, H 2.76, N 6.83, S 23.67.

2.2.3 3-(8-Chloro-4*H*-thiochromeno[4,3-*d*]thiazol-2-yl)-2-(4-nitrophenyl)thiazolidin-4-one (3c)

Yield 88% of red solid, m.p. 198-199 °C, UV-vis (MeOH) $\lambda_{\max}$: 240 nm; IR (KBr) ν : 1685, 1620, 3078, 1517, 1458, 1344, 829 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ : 3.96 (d, J = 16.47 Hz, 1H, COCH₂S), 4.09 (d, J = 15.16 Hz, 1H, COCH₂S), 4.11-4.18 (m, 2H, SCH₂), 6.74 (s, 1H, NCHS), 7.10 (dd, J = 8.32, 2.37 Hz, 1H, Ar-H), 7.19 (d, J = 8.30 Hz, 1H, Ar-H), 7.46 (d, J = 2.31 Hz, 1H, Ar-H), 7.57 (d, J = 8.77 Hz, 2H, Ar-H), 8.27 (d, J = 8.77 Hz, 2H, Ar-H); MS (APCI) m/z : 461.8 (M+H)⁺, 463.8 (M+2+H)⁺. Anal. Calcd for C₁₉H₁₂ClN₃O₃S₃: C 49.40, H 2.62, N 9.10, S 20.82; Found C 49.36, H 2.58, N 9.06, S 20.79.

2.2.4 3-(8-Chloro-4*H*-thiochromeno[4,3-*d*]thiazol-2-yl)-2-phenylthiazolidin-4-one (3d)

Yield 63% of yellow solid, m.p. 183-186 °C, UV-vis (MeOH) $\lambda_{\max}$: 238 nm; IR (KBr) ν : 3029, 1685, 1621, 1490, 1456 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ : 3.87 (d, J = 16.44 Hz, 1H, COCH₂S), 4.03 (d, J = 15.10 Hz, 1H, COCH₂S), 4.09-4.16 (m, 2H, SCH₂), 6.67 (d, J = 0.86 Hz, 1H, NCHS), 7.07 (dd, J = 8.31, 2.37 Hz, 1H, Ar-H), 7.15 (d, J = 8.30 Hz, 1H, Ar-H), 7.28-7.32 (m, 1H, Ar-H), 7.35-7.39 (m, 4H, Ar-H); MS (APCI) m/z : 416.8 (M+H)⁺, 418.8 (M+2+H)⁺. Anal. Calcd for C₁₉H₁₃ClN₂O₂S₃: C 54.73, H 3.14, N 6.72, S 23.07; Found C 54.67, H

3.09, N 6.69, S 23.11.

2.2.5 3-(8-Chloro-4H-thiochromeno[4,3-d]thiazol-2-yl)-2-(4-(dimethylamino)phenyl)thiazolidin-4-one (3e)

Yield 55% of pale yellow solid, m.p. 129-131 °C, UV-vis (MeOH) λ_{max} : 240 nm; IR (KBr) ν : 2967, 2855, 1685, 1620, 1588, 1490, 1460, 1450, 1385 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ : 3.08 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 3.86 (d, $J=16.44$ Hz, 1H, COCH_2S), 4.06 (d, $J=28.16$ Hz, 1H, COCH_2S), 4.15 (s, 2H, SCH_2), 6.62 (s, 1H, NCHS), 6.69 (d, $J=10.27$ Hz, 1H, Ar-H), 6.73 (d, $J=8.85$ Hz, 1H, Ar-H), 7.10 (dd, $J=20.48$, 2.26 Hz, 1H, Ar-H), 7.18 (d, $J=24.94$ Hz, 1H, Ar-H), 7.30 (d, $J=8.73$ Hz, 1H, Ar-H), 7.74 (d, $J=8.75$ Hz, 1H, Ar-H), 7.87 (d, $J=8.47$ Hz, 1H, Ar-H); MS (APCI) m/z : 459.8 ($\text{M}+\text{H}$) $^+$, 461.8 ($\text{M}+2+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{ClN}_3\text{OS}_3$: C 54.83, H 3.94, N 9.13, S 20.91; Found C 54.79, H 3.87, N 9.09, S 20.96.

2.2.6 3-(8-Chloro-4H-thiochromeno[4,3-d]thiazol-2-yl)-2-(4-chlorophenyl)thiazolidin-4-one (3f)

Yield 86% of brown solid, m.p. 147-151 °C, UV-vis (MeOH) λ_{max} : 238 nm; IR (KBr) ν : 1697, 1621, 1521, 1488, 1458 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ : 3.77 (d, $J=16.03$ Hz, 1H, COCH_2S), 4.04-4.10 (m, 2H, SCH_2), 4.29 (d, $J=15.96$ Hz, 1H, COCH_2S), 6.32 (s, 1H, NCHS), 6.42 (d, $J=3.12$ Hz, 1H, Ar-H), 6.73 (s, 1H, Ar-H), 7.09 (d, $J=7.18$ Hz, 1H, Ar-H), 7.25 (d, $J=9.11$ Hz, 2H, Ar-H), 7.35 (s, 1H, Ar-H), 7.44 (d, $J=10.19$ Hz, 1H, Ar-H); MS (APCI) m/z : 450.8 ($\text{M}+\text{H}$) $^+$, 452.8 ($\text{M}+2+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{19}\text{H}_{12}\text{Cl}_2\text{N}_2\text{OS}_3$: C 50.55, H 2.68, N 6.21, S 21.31; Found C 50.49, H 2.62, N 6.26, S 21.28.

2.2.7 2-(Benzo[d][1,3]dioxol-5-yl)-3-(8-chloro-4H-thiochromeno[4,3-d]thiazol-2-yl)-thiazolidin-4-one (3g)

Yield 48% of pale brown solid, m.p. 154-157 °C, UV-vis (MeOH) λ_{max} : 240 nm; IR (KBr) ν : 3080, 2923, 2854, 1683, 1625, 1588, 1521, 1488, 1338, 1245, 1033 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ : 3.89 (d, $J=16.47$ Hz, 1H, COCH_2S), 4.07 (d, $J=15.08$ Hz, 1H, COCH_2S), 4.19-4.12 (m, 2H, SCH_2), 5.97 (dd, $J=9.16$, 1.22 Hz, 2H, OCH_2O), 6.62 (s, 1H, NCHS), 6.80 (d, $J=8.05$ Hz, 1H, Ar-H), 6.85 (d, $J=1.67$ Hz, 1H, Ar-H), 6.93 (dd, $J=8.07$, 1.67 Hz, 1H, Ar-H), 7.11 (dd, $J=8.31$, 2.36 Hz, 1H, Ar-H), 7.19 (d, $J=8.30$ Hz, 1H, Ar-H), 7.62 (d, $J=2.29$ Hz, 1H, Ar-H); MS (APCI) m/z : 460.8 ($\text{M}+\text{H}$) $^+$, 462.8 ($\text{M}+2+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S}_3$: C 52.11, H 2.84, N 6.08, S 20.87; Found C 52.08, H 2.79, N 6.12, S 20.83.

2.2.8 2-(Furan-2-yl)-3-(8-methyl-4H-thiochromeno[4,3-d]thiazol-2-yl)thiazolidin-4-one (3h)

Yield 62% of brown solid, m.p. 163-165 °C, UV-vis (MeOH) λ_{max} : 238 nm; IR (KBr) ν : 2923, 2852, 1687, 1621, 1588, 1521, 1506, 1488, 1288, 1338 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ : 2.38 (s, 3H, CH_3), 3.79 (d, $J=15.98$ Hz, 1H, COCH_2S), 4.09 (m, 2H, SCH_2), 4.30 (d, $J=16.14$ Hz, 1H, COCH_2S), 6.34 (dd, $J=3.21$, 1.82 Hz, 1H, furan-H), 6.44 (d, $J=3.22$ Hz, 1H, furan-H), 6.81 (s, 1H, NCHS), 7.00 (dd, $J=7.88$, 1.29 Hz, 1H, Ar-H), 7.20 (d, $J=7.89$ Hz, 1H, Ar-H), 7.38 (d, $J=1.01$ Hz, 1H, furan-H), 7.65 (s, 1H, Ar-H); MS (APCI) m/z : 386.8 ($\text{M}+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_3$: C 55.93, H 3.65, N 7.25, S 24.89; Found C 55.89, H 3.60, N 7.20, S 24.80.

2.2.9 3-(8-Fluoro-4H-thiochromeno[4,3-d]thiazol-2-yl)-2-(furan-2-yl)thiazolidin-4-one (3i)

Yield 64% of brown solid, m.p. 176—179 °C, UV-vis (MeOH) λ_{max} : 234 nm; IR (KBr) ν : 1683, 1615, 1521, 1506, 1288 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ : 3.77 (d, $J=16.06$ Hz, 1H, COCH_2S), 4.14-4.04 (m, 2H), 4.28 (d, $J=16.13$ Hz, 1H, COCH_2S), 6.33 (dd, $J=3.28$, 1.84 Hz, 1H, furan-H), 6.43 (d, $J=3.25$ Hz, 1H, furan-H), 6.74 (s, 1H, NCHS), 7.11 (dd, $J=8.32$, 2.39 Hz, 1H, Ar-H), 7.20 (d, $J=8.31$ Hz, 1H, Ar-H), 7.36 (d, $J=1.08$ Hz, 1H, furan-H), 7.76 (d, $J=2.32$ Hz, 1H, Ar-H); MS (APCI) m/z : 390.8 ($\text{M}+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{17}\text{H}_{11}\text{FN}_2\text{O}_2\text{S}_3$: C 52.29, H 2.84, N 7.17, S 24.64; Found C 52.23, H 2.90, N 7.22, S 24.60.

2.2.10 3-(7-Fluoro-8-methyl-4H-thiochromeno[4,3-d]thiazol-2-yl)-2-(furan-2-yl)thiazolidin-4-one (3j) Yield 61% of brown solid, m.p. 169-172 °C, UV-vis (MeOH) λ_{max} : 238 nm; IR (KBr) ν : 2923, 2852, 1683, 1622, 1588, 1506, 1466, 1388, 1280 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ : 2.27 (s, 3H, CH_3), 3.79 (d, $J=16.03$ Hz, 1H, COCH_2S), 4.15-4.05 (m, 2H, SCH_2), 4.31 (d, $J=15.98$ Hz, 1H, COCH_2S), 6.34 (dd, $J=3.07$, 1.87 Hz, 1H, furan-H), 6.45 (d, $J=3.24$ Hz, 1H, furan-H), 6.76 (s, 1H, NCHS), 7.12 (d, $J=7.22$ Hz, 1H, furan-H), 7.38 (s, 1H, Ar-H), 7.46 (d, $J=10.26$ Hz, 1H, Ar-H); MS (APCI) m/z : 404.8 ($\text{M}+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{FN}_2\text{O}_2\text{S}_3$: C 53.45, H 3.24, N 6.93, S 23.78; Found C 53.40, H 3.20, N 6.97, S 23.74.

2.3 Preparation of compounds 4

Compound 3 (1.00 mmol) was dissolved in the THF (10 mL) and cooled to 0 °C, then added NaH (2.50 mmol). After stirring about 10 min, aromatic aldehyde (1.10 mmol) added to the solution. Keeping the reaction at room temperature over 2 h, then the mixture was cooled to 0 °C and poured into water (4 mL). After the solution was extracted with ethyl acetate, the organic layer was dried over anhydrous MgSO_4 . Solvent was removed under reduced presser to provide a crude product which was purified by column chromatography (silica-gel,

dichloromethane: petrol- eum=1:8-1:1(v/v)) to afford pure 4.

2.3.1 3-(8-Chloro-4H-thiochromeno[4,3-d]thiazol-2-yl)-2-(furan-2-yl)-5-(furan-2-ylmethylene)thiazolidin-4-one (4)

Yield 80% of green solid, m.p. 220-223 °C, UV-vis (MeOH) $\lambda_{\max}$: 245 nm; IR (KBr) ν : 1685, 1621, 1588, 1506, 1466, 1280 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ : 4.08 (d, J = 15.04 Hz, 1H, SCH_2), 4.14 (d, J = 15.03 Hz, 1H, SCH_2), 6.33 (dd, J = 9.57, 3.17 Hz, 1H, furan-H), 6.55-6.49 (m, 2H, furan-H), 6.66 (d, J = 3.44 Hz, 1H, furan-H), 6.88 (s, 1H, NCHS), 7.09 (dd, J = 8.29, 2.26 Hz, 1H, Ar-H), 7.18 (d, J = 8.28 Hz, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.54 (d, J = 8.61 Hz, 1H, furan-H), 7.59 (s, 1H, Ar-H), 7.72 (d, J = 2.24 Hz, 1H, furan-H); MS (APCI) m/z : 484.7 ($\text{M}+\text{H}$) $^+$, 486.7 ($\text{M}+2+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{22}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S}_3$: C 54.48, H 2.70, N 5.78, S 19.83; Found C 54.43, H 2.67, N 5.82, S 19.79.

2.4 Anticancer Activity in Vitro

The anticancer activities of target compounds were evaluated in vitro gastric cancer cells (SGC-7901), cervical cancer cells (Hela) and lung cancer cells (A-549) by measuring cell viability according to the MTT method described in the literature with cisplatin as the positive control. The cells were seeded in RPMI 1640 medium (100 μL) in a 96-well plate at a concentration of 6000-7000 cells per well. After culturing for 12 h at 37 °C and 5% CO_2 , cells were incubated with various concentrations of the samples for 24 h. Twenty microliter of MTT (5 mg/mL) was added and incubated with the cells for 4 h. The formazan product was dissolved by adding dimethyl sulfoxide (DMSO, 100 μL) to each well, and the plates were read at 570 nm. All measurements were performed in triplicate and each experiment was repeated at least three times. IC_{50} values were determined as the drug and sample concentration at 50% inhibition of the cell growth.

3. Results and discussion

3.1 Microwave-assisted synthesis thiazolidin-4-ones

Generally, 1,3-thiazolidin-4-ones derivatives can be synthesized by a three-component condensation of a primary amine, an aldehyde, and mercaptoacetic acid. The dehydration process is the rate determining step of the reaction which is usually performed, the reaction is usually performed in refluxing toluene with dehydrating agents for 2-48 hours, but the yields were generally not satisfactory. Thus either a catalyst or a dehydrating agent or a Dean and Stark' was usually used to promote reaction. The applications of some new synthetic methods, such as microwave-assisted synthesis, and reagents, such as ionic liquids (Zhang, Xinying, 2009), and KSF clay (Dandia, A., 2006), have been recently explored for improving the synthesis of the 1,3-thiazolidin-4-ones. We now reported a new method for one-pot synthesis of a series of new 1,3-thiazolidin-4-ones using DCC as a dehydrating agent under microwave heating in a sealed vessel (Scheme 1).

This new method resulted in increased yields with shorter reaction times in comparison with the conventional routes which typically affords yields in the range 10%-65%. As to different substitutions of aromatic aldehydes $\text{R}_2\text{-CHO}$, their reactivity was: $\text{R}_2=\text{aryl}$ with electron withdrawing > aryl with no substitution > aryl with electron donating. The yields were good when aromatic aldehydes with electron withdrawing, such as $-\text{NO}_2$ and $-\text{Cl}$, and it was more than 85%; when $\text{R}_2=4\text{-nitrophenyl}$, the yield was the best. When aromatic aldehydes with electron donating, mainly because electron donating groups increased the electron density reducing the reactivity of carbonyl, so the reactivity lower, the yield decreased. In this report, we also studied the effects of different substituents on 4H-thiochromeno[4,3-d]thiazol-2-amines. The results showed that different R and R_1 had no significant impact on the yield of 1,3-thiazolidin-4-one.

In conclusion, during the microwave-assisted synthesis of 1,3-thiazolidin-4-ones, the electron density of aldehydes had great impact on the reactivity. Generally speaking, the reactivity was higher when aromatic aldehydes with electron withdrawing, and the yield was also good; when electron donating on aromatic ring, the reactivity was lower, so the yield decreased.

3.2 Study for anticancer activity

Anticancer activities were tested against gastric cancer cells (SGC-7901), cervical cancer cells (Hela) and lung cancer cells (A-549) and using cisplatin as positive control (Table 1). Most of the compounds had good anticancer activities. R_2 had significant impact on the anticancer activity. The R_2 with deactivating groups, such as $\text{R}_2=4\text{-nitrophenyl}$ and 4-chlorophenyl (compounds 3c and 3f) had better anticancer activity than that had activating groups or no substitutions. When R_2 was maintained, different R and R_1 had no significant impact on the anticancer activity. Moreover it was worth noting that the anticancer activity was better when R_2 was heterocyclic than R_2 was benzene ring's. In addition, the further molecular modifications on

1,3-thiazolidin-4-one brought us better result and methylene at C-5 position of 1,3-thiazolidin-4-one showed the best anticancer activity.

In summary, a series of new 1,3-thiazolidin-4-ones synthesized under microwave-assisted with DCC as dehydrating agent were reported. In microwave-assisted synthesis conditions, the yields of the new compounds were better than conventional method and the reaction time in 10 minutes. Most of the new compounds had anticancer activity, compound had the best anticancer activity when a furan-2-yl was at C-2 position and a methylene was at C-5 position, so it may be noted that different heteroaryl substituents at C-2 position and methylene at C-5 position of 1,3-thiazolidin-4-ones deserve further consideration from the point of structure-activity optimization. Further structure-activity optimization and other biological studies of 1,3-thiazolidin-4-ones are undertook in the laboratory.

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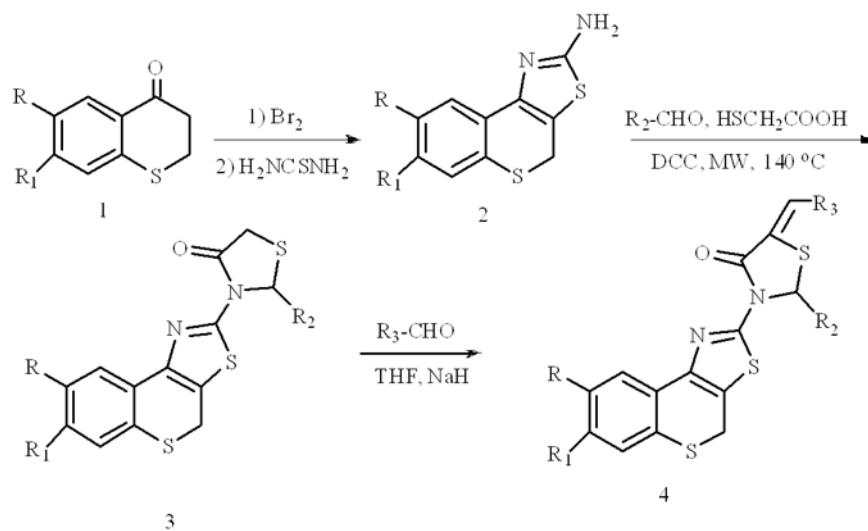
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Table 1. Anticancer activity of compounds synthesized

Compounds	IC ₅₀ (μM)		
	SGC-7901	Hela	A-549
3a	17.60	19.00	19.60
3b	8.35	8.85	9.58
3c	12.78	14.08	13.43
3d	17.00	16.55	18.95
3e	16.00	17.66	18.79
3f	10.42	10.20	10.92
3g	19.34	20.39	19.31
3h	9.08	9.00	10.01
3i	9.89	8.90	9.79
3j	9.97	9.10	10.04
4	5.76	6.19	6.67
Cisplatin	5.05	4.66	7.70



1a: R=Cl, R₁=H, 1b: R=CH₃, R₁=H, 1c: R=F, R₁=H, 1d: R=CH₃, R₁=F
 2a: R=Cl, R₁=H, 2b: R=CH₃, R₁=H, 2c: R=F, R₁=H, 2d: R=CH₃, R₁=F

3a: R=Cl, R₁=H, R₂=4-methoxyphenyl, 3b: R=Cl, R₁=H, R₂=furan-2-yl, 3c: R=Cl, R₁=H, R₂=4-nitrophenyl,
 3d: R=Cl, R₁=H, R₂=phenyl, 3e: R=Cl, R₁=H, R₂=4-(dimethylamino)phenyl, 3f: R=Cl, R₁=H, R₂=4-chlorophenyl,
 3g: R=Cl, R₁=H, R₂=benzo[d][1,3]dioxole-5-yl, 3h: R=CH₃, R₁=H, R₂=furan-2-yl, 3i: R=F, R₁=H, R₂=furan-2-yl,
 3j: R=CH₃, R₁=F, R₂=furan-2-yl

4: R=Cl, R₁=H, R₂=furan-2-yl, R₃=furan-2-yl

Scheme 1. The synthesis route of target compound