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Synthesis and antitumor activities of a new series of 4,5-dihydro-1*H*-thiochromeno[4,3-*d*]pyrimidine derivatives

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Received April 22, 2011; accepted May 27, 2011; published online January 5, 2012

A new series of 4,5-dihydro-1*H*-thiochromeno[4,3-*d*]pyrimidine derivatives have been designed and synthesized. The antitumor activities of the target compounds have been evaluated *in vitro* against two human cancer cell lines including A549 (human alveolar adenocarcinoma cell) and H460 (human lung cancer) by MTT assay. Most of the target compounds exhibited significant antitumor activities against A549 and H460 cancer cell lines. The most potent compound 4-(benzo[d][1,3]dioxol-5-yl)-8,9-difluoro-2-(4-methylpiperazin-1-yl)-4,5-dihydro-1*H*-thiochromeno[4,3-*d*]pyrimidine (CH05) (IC₅₀ = 0.44 μ M, 3.07 μ M) was 2.0 and 8.4 times more active than gefitinib (IC₅₀ = 0.89 μ M, 16.81 μ M) against A549 and H460 cell lines, respectively.

heterocycle, synthesis, 4,5-dihydro-1H-thiochromeno[4,3-d]pyrimidine derivatives, antitumor activity

1 Introduction

Cancer is a class of diseases in which a group of cells display uncontrolled growth, invasion that intrudes upon and destroys adjacent tissues, and sometimes metastasis, i.e. spreading to other locations in the body via lymph or blood. Existing cancer solutions include chemotherapy, radiation therapy, surgery, immunotherapy, monoclonal antibody therapy and other methods. The most common way for cancer treatment is based on the conventional chemotherapy [1]. The molecules with quinazoline scaffold and thiochroman-4-one ring are potential anticancer agents to be developed as new drugs for chemotherapy.

The quinazoline scaffold is of great importance to chemists and biologists as it is available in a large variety of naturally occurring compounds [2]. It is also found in clinically useful molecules with diverse biological activities, such as antiviral, antimalarial, anticonvulsant, antibacterial, diuretic, hypnotic, hypoglycaemic, antitumor and antihypertensive activities[3, 4]. It has been known that the 4,5-dihydro-1*H*-thiochromeno[4,3-*d*]pyrimidine derivatives exhibited various biological activities including anticancer, antiinflammatory, antifungal and herbicidal activities [5–7].

The thiochroman-4-one ring moiety belongs to the privileged structure in modern medicinal chemistry, particularly in the discovery of new antitumor and antiangiogenic agents [8, 9]. In recent years, it has been found that the quinazoline-2(1H)-thione analogues which were obtained by the high-throughput screening had good anti-Bcl-2 activity [10]. Due to both the importance of thiochroman derivatives and the issues associated with their synthesis, we have directed our efforts toward the development of effective methods for the synthesis of these compounds. In this report, a series of the 4,5-dihydro-1*H*-thiochromeno [4,3-d]pyrimidine derivatives were designed and synthesized based on (i) the analysis of the structure-activity relationship of the quinazoline-2(1H)-thione derivatives, (ii) quinazoline-2(1H)-thione as the lead compound, and (iii) the combined principle of bioisosterism and hybridization. The in vitro antitumor ac-

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tivities of the target compounds were evaluated.

2 Experimental

2.1 Chemistry

All reagents and solvents were obtained from commercial suppliers and used without purification. Melting points were determined by the capillary tube method and the melting point instrument was uncorrected. Mass spectra (MS) were recorded in ESI mode on the Agilent 1100LC-MS spectrometer (Agilent, Palo Alto, CA, USA). IR spectra were recorded in the range of 4000–400 cm⁻¹ using KBr pellets on a Bruker AFS55 spectrometer. ¹H NMR spectra were performed on a Bruker spectrometer (Bruker Bioscience, Billerica, MA, USA) operating at 300 MHz in DMSO- d_6 with TMS as the internal standard. ¹³C NMR spectra were performed on the same Bruker spectrometers operating at 75 MHz in DMSO- d_6 with TMS as the internal standard. The microwave irradiated reactions were performed in a Yuhua WBFY-201 domestic household microwave oven.

Synthesis of 3-(arylthio)propa-noic acids (3)

The solution of thiophenol (1) (0.5 mol) in aqueous KOH (10%, 250 mL) and EtOH (300 mL) was mixed with 3-chloropropanoic acid (0.5 mol) in the saturated aqueous solution of K_2CO_3 (0.5 mol). The resulting mixture was refluxed for 5 h, cooled to room temperature, concentrated under vacuum, and neutralized with 18% HCl solution until pH 3. The resulting precipitate was filtered and washed sequentially with water (20 mL) and petroleum ether (20 mL) to give 3-(arylthio)propanoic acid (3) as a white solid.

3-(2-Methoxyphenylthio)propanoic acid (**3a**). White solid, 66% yield; mp: 91–92 °C (lit. [11] 92–93 °C). ESI-MS (*m/z*): 234.9 ([M+Na]⁺), 251.0 ([M+K]⁺).

3-(4-Fluorophenylthio)propanoic acid (**3b**). White solid, 90% yield; mp: 75–76 °C (lit [10] 75–76 °C). ESI-MS (*m/z*): 222.9 ([M+Na]⁺), 239.0 ([M+K]⁺).

3-(3,4-Difluorophenylthio)propanoic acid (**3c**). White solid, 90% yield; mp: 92–93 °C. ESI-MS (m/z): 241.0 ([M+Na]⁺), 256.9 ([M+K]⁺).

Synthesis of 3,4-dihydro-2H-1-benzothiopyran-4-ones (4)

According to the reported procedure [12], 3-(arylthio) propanoic acid (**3**) (0.2 mol) was dissolved in concentrated H_2SO_4 (200 mL) at 5 °C and set aside overnight. Then 200 g ice was poured in, and cooled for 1 h. The solid was filtered and recrystallized from petroleum ether to give 3,4-dihydro-2*H*-1-benzothiopyran-4-one (**4**).

8-Methoxy-3,4-dihydro-2*H*-1-benzothiopyran-4-one (**4a**). White solid, 75% yield; mp: 60–61 °C. ESI-MS (m/z): 216.9 ([M+Na]⁺), 232.9 ([M+K]⁺).

6-Fluoro-3,4-dihydro-2*H*-1-benzothiopyran-4-one (**4b**). White solid, 80% yield; mp: 96–97 °C (lit. [13] 96–97 °C).

ESI-MS (m/z): 205.0 ([M+Na]⁺).

6,7-Difluoro-3,4-dihydro-2*H*-1-benzothiopyran-4-one (**4c**). White solid, 66% yield; mp: 101-102°C. ESI-MS (m/z): 223.0 ([M+Na]⁺).

Synthesis of 2-methyl-2-thiopseudourea sulfate (6)

A mixture of thiourea (5) (7.6 g, 0.1 mol), TEBA (0.2 g, 0.01 mol), $(CH_3O)_2SO_2$ (12.6 g, 0.1 mol), and water (50 mL) was refluxed for 6 h and the reaction was monitored by TLC. After cooling to room temperature, the precipitated product was filtered off and washed with ethanol to give 6 as a white solid in 78% yield.

Synthesis of aminocarboximidamides (7)

A solution of 2-methyl-2-thiopseudourea sulfate (1.4 g, 5 mmol), and organic amine (5 mmol) in water (20 mL) was heated under reflux for 2 h. Then a solution of barium chloride (1.0 g, 5 mmol) in water (12.5 mL) was added dropwise to the reaction mixture over 30 min. After addition, the reaction mixture was refluxed for 1 h and then allowed to cool to room temperature. After cooling and filtration, the filtrate was concentrated leaving a syrup, dissolved in ethanol (5 mL), and the resulting solution was stripped. The obtained solid was recrystallized from methanol.

Piperidine-1-carboximidamide (7a). White solid, 68% yield; mp: 158–159 °C. ESI-MS (m/z): 128.1 $([M+H]^+)$.

Morpholine-4-carboximidamide (**7b**). White solid, 88% yield; mp: 138–139 °C (lit. [14] 138–139 °C). ESI-MS (m/z): 130.1 ([M+H]⁺).

4-Methylpiperazine-1-carboximidamide (**7c**). White solid, 78% yield; mp: 148–149 °C. ESI-MS (m/z): 143.0 ($[M+H]^+$).

4-Benzylpiperazine-1-carboximidamide (**7d**). White solid, 70% yield; mp: 184–185 °C. ESI-MS (m/z): 219.0 ($[M+H]^+$).

4-(4-Methoxyphenyl)piperazine-1-carboximidamide (7e). White solid, 78% yield; mp: 145–146 °C. ESI-MS (m/z): 234.9 ($[M+H]^+$).

Synthesis of 4,5-dihydro-1H-thiochromeno[4,3-d]pyrimidines (CH01-CH11)

A mixture of aldehyde (8) (0.01 mol), ketone (4) (0.01 mol), and aminocarboximidamide (7) (0.01 mol) was subjected to microwave heating for 5 min using acetonitrile (5 mL) as the energy transfer medium and the KOH aqueous solution (0.5 mL) as the catalyst. The reaction mixture was allowed to stand at room temperature for a few hours. Upon completion of the reaction as monitored by TLC, the solvent was removed by distillation, and the resulting mixture was adjusted to pH 7 with AcOH at 10 °C. The precipitate was collected by filtration, and purified by silica gel column chromatography (eluent : CH₂Cl₂-MeOH, 9:1) to give the 4,5-dihydro-1*H*-thiochromeno[4,3-*d*]pyrimidine derivatives as the target compounds.

8,9-Difluoro-2-(4-(4-methoxyphenyl)piperazin-1-yl)-4phenyl-4,5-dihydro-1*H*-thiochromeno[4,3-d]pyrimidine (**CH01**). Yield: 45%. mp: 195–196 °C; ESI-MS (*m/z*): 504.9, 505.9; IR (KBr, cm⁻¹): 3420.0, 2840.4, 1591.0, 1512.7, 1300.9, 1249.3, 1033.7; ¹H NMR (DMSO-*d*₆, 300 MHz) & 2.96–3.06 (m, 4H), 3.13–3.18 (m, 2H), 3.48–3.53 (m, 4H), 3.68 (s, 3H), 5.02 (s, 1H), 6.84 (d, 1H, *J* = 9 Hz), 6.93 (d, 2H, *J* = 9 Hz), 7.27–7.37 (m, 5H), 7.39 (s, 1H), 7.48 (d, 1H, *J* = 2.7 Hz), 7.86 (dd, 1H, *J*₁ = 3.9 Hz, *J*₂ = 12 Hz), 10.20 (s, 1H).

4-(Benzo[d][1,3]dioxol-5-yl)-8,9-difluoro-2-(4-(4-methoxyphenyl)piperazin-1-yl)-4,5-dihydro-1*H*-thiochromeno [4,3-*d*]pyrimidine (**CH02**). Yield: 56%. mp: 155–157 °C; ESI-MS (*m/z*): 548.8, 548.6; IR (KBr, cm⁻¹): 3412.3, 2891.5, 1593.8, 1512.9, 1342.3, 1248.3, 1037.0; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.97–3.05 (m, 4H), 3.13–3.18 (m, 1H), 3.48–3.54 (m, 4H), 3.68 (s, 3H), 4.95 (s,1H), 5.98 (s, 2H), 6.83–6.93 (m,6H), 7.31 (dd, 1H, *J*₁ = 3.3 Hz, *J*₂ = 10.2 Hz), 7.45 (d, 1H, *J* = 3.3 Hz), 7.86 (dd, 1H, *J*₁ = 9 Hz, *J*₂ = 12 Hz), 9.80 (s,1H).

9-Fluoro-2-(piperidin-1-yl)-4-(3,4,5-trimethoxyphenyl)-4, 5-dihydro-1*H*-thiochromeno[4,3-d]pyrimidine (**CH03**). Yield: 52%. mp: 180–181 °C; ESI-MS (*m/z*): 469.9, 471.8; IR (KBr, cm⁻¹): 3397.2, 2935.4, 1592.0, 1555.5, 1323.9, 1236.2, 1127.2; ¹H NMR (DMSO- d_6 , 300 MHz) δ : 1.41–1.54 (m, 6H), 3.15–3.31 (m, 2H), 3.43 (s, 4H), 3.62 (s, 3H), 3.73 (s, 6H), 4.95 (s, 1H), 6.73 (s, 1H), 6.97 (d, 1H, *J* = 6 Hz), 7.2 (m, 2H), 7.63 (d, 1H, *J*=9 Hz), 10.19 (s, 1H); ¹³C NMR (DMSO- d_6 , 75 MHz): δ 153.6, 153.4, 142.9, 140.9, 137.5, 137.0, 128.5, 127.6, 114.7, 114.4, 112.5, 112.2, 104.5, 60.6, 58.2, 56.5, 47.0, 27.1, 26.1, 25.0.

4-(8,9-Difluoro-4-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-thiochromeno[4,3-d]pyrimidin-2-yl)morpholine (**CH04**). Yield: 49%. mp: 115–116 °C; ESI-MS (*m/z*): 490.3, 491.3; IR (KBr, cm⁻¹): 3397.8, 2963.8, 1593.8, 1563.8, 1351.9, 1233.2, 1125.4; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 3.15–3.23 (m, 2H), 3.34–3.48 (m, 4H), 3.52–3.61 (m, 4H), 3.63 (s, 3H), 3.74 (s, 6H), 5.01 (s, 1H), 6.71 (s, 1H), 7.32 (dd, 1H, *J*₁ = 10 Hz, *J*₂ = 12 Hz), 7.37 (s,1H), 7.82 (dd,1, *J*₁ = 8 Hz, *J*₂ = 12 Hz), 10.19 (s,1H).

4-(Denzo[d][1,3]dioxol-5-yl)-8,9-difluoro-2-(4-methylpiperazin-1-yl)-4,5-dihydro-1*H*-thiochromeno[4,3-d]pyrimidine (**CH05**). Yield: 55%. mp: 201–202 °C; ESI-MS (*m/z*): 456.8, 457.8; IR (KBr, cm⁻¹): 3448.8, 2934.6, 1593.3, 1556.7, 1347.3, 1292.2, 1151.2; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.17 (s, 3H), 2.22–2.34 (m, 4H), 3.12–3.17 (m, 2H), 3.36–3.44 (m, 4H), 4.92 (s,1H), 5.98 (s, 2H), 6.81–6.88 (m, 2H), 7.30 (dd, 1H, *J*₁ = 6.6 Hz, *J*₂ = 10.8 Hz), 7.33 (s, 1H), 7.82 (dd, 1H, *J*₁ = 3.3 Hz, *J*₂ = 12.6 Hz), 10.20 (s, 1H); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 153.4, 148.2, 147.4, 139.4, 136.1, 128.9, 127.7, 120.5, 115.8, 115.5, 114.5, 114.3, 108.8, 107.7, 104.3, 101.7, 57.9, 55.1, 46.5, 45.2, 26.9.

8,9-Difluoro-2-(4-(4-methoxyphenyl)piperazin-1-yl)-4-(3, 4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-thiochromeno[4,3-d]pyrimidine (**CH06**). Yield: 61%. mp: 209–213 °C; ESI-MS (*m/z*): 595.2, 596.2; IR (KBr, cm⁻¹): 3442.4, 2937.7, 1590.7, 1510.5, 1305.8, 1248.8, 1126.3; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.97–3.06 (m, 4H), 3.13–3.18 (m, 2H), 3.54–3.59 (m, 4H), 3.62 (s, 3H), 3.68 (s, 3H), 3.72 (s, 6H), 5.01 (s, 1H), 6.72 (s, 2H), 6.81–6.93 (m, 4H), 7.33 (dd, 1H, *J*₁= 7.8 Hz, *J*₂= 10.5 Hz), 7.46 (s, 1H), 7.85 (dd, 1H, *J*₁= 9 Hz, *J*₂= 12.3 Hz), 10.20 (s. 1H); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 153.9, 153.6, 149.5, 148.1, 146.3 146.0, 140.6, 137.5, 136.6, 136.5, 129.1, 120.9, 118.5,115.0, 104.5, 58.1, 57.3, 56.5, 55.9, 51.1, 50.4, 45.6, 27.0.

2-(4-Benzylpiperazin-1-yl)-8,9-difluoro-4-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-thiochromeno[4,3-d]pyrimidine (**CH07**). Yield: 57%. mp: 212–213 °C; ESI-MS (*m/z*): 578.9, 579.9; IR (KBr, cm⁻¹): 3427.1, 2940.1, 1591.2, 1488.9, 1303.8, 1232.7, 1128.2; ¹H NMR (DMSO- d_6 , 300 MHz) δ : 2.34–2.39 (m, 4H), 3.13–3.18 (m, 2H), 3.39–3.52 (m, 4H), 3.63 (s, 3H), 3.73 (s, 6H), 3.82 (s, 2H), 4.97 (s, 1H), 6.70 (s, 2H), 7.25–7.32 (m, 5H), 7.65–7.77 (m, 2H), 10.20 (s. 1H).

8,9-Difluoro-2-(piperidin-1-yl)-4-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-thiochromeno[4,3-d]pyrimidine (**CH08**). Yield: 48%. mp: 94–95 °C; ESI-MS (*m/z*): 487.9, 488.9; IR (KBr, cm⁻¹): 3464.2, 2934.7, 1593.9, 1562.8, 1350.2, 1233.4, 1126.0; ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 1.47–1.57 (m, 6H), 3.21–3.32 (m, 2H), 3.47 (s, 4H), 3.64 (s, 3H), 3.74 (s, 6H), 5.00 (s, 1H), 6.76 (s, 2H), 7.36–7.42 (m, 1H), 7.72–7.79 (m, 1H), 10.20 (s, 1H); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ: 153.6, 153.4, 143.3 140.8, 137.5, 136.6, 136.5, 129.0, 115.9, 114.5, 114.2, 104.5, 60.7, 58.0, 56.5, 46.4, 27.1, 26.1, 24.9.

2-(4-Benzylpiperazin-1-yl)-7-methoxy-4-phenyl-4,5dihydro-1*H*-thiochromeno[4,3-d]pyrimidine (**CH09**). Yield: 45%. mp: 150–152 °C; ESI-MS (*m/z*): 483.3, 485.3; IR (KBr, cm⁻¹): 3426.0, 2931.4, 1593.1, 1529.1, 1353.0, 1236.1, 1134.0; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.34–2.39 (m, 4H), 3.13–3.18 (m, 2H), 3.41–3.48 (m, 6H), 3.71 (s, 3H), 4.95 (s, 1H), 6.69 (d, 2H, *J* = 9 Hz), 7.25–7.35 (m, 10H), 7.82 (d, 1H, *J* = 8.4 Hz), 10.20 (s, 1H).

4-(7-Methoxy-4-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-thiochromeno[4,3-d]pyrimidin-2-yl)morpholine (**CH10**). Yield: 46%. mp : 113–115 °C; ESI-MS (*m/z*): 483.9, 484.9; IR (KBr, cm⁻¹): 3386.3, 2935.9, 1594.8, 1566.9, 1348.4, 1266.8, 1126.8; ¹H NMR (DMSO- d_6 , 300 MHz) δ : 3.12–3.17 (m, 2H), 3.34–3.46 (m, 4H), 3.53–3.60 (m, 4H), 3.63 (s, 3H), 3.72 (s, 3H), 3.74 (s, 6H), 4.97 (s, 1H), 6.70 (d, 1H, *J* = 8.4 Hz), 6.73 (s, 2H), 7.28 (s, 1H), 7.82 (d, 1H, *J* = 8.4Hz), 10.20 (s, 1H).

4-(8,9-Difluoro-4-phenyl-4,5-dihydro-1*H*-thiochromeno [4,3-d]pyrimidin-2-yl)morpholine (CH11). Yield: 47%. mp:

190–192 °C; ESI-MS(μ/ζ): 502.9, 503.9; IR (KBr, cm⁻¹): 3335.3, 2977.3, 1588.2, 1552.8, 1392.1, 1273,2, 1120.9; ¹H NMR (DMSO- d_6 , 300 MHz) δ: 2.17 (s, 3H), 2.28–2.50 (m, 4H), 3.19–3.24 (m, 2H), 3.41–3.53 (m, 4H), 3.63 (s, 3H), 3.74 (s, 6H), 4.97 (s, 1H), 6.71 (s, 2H), 7.26–7.32 (dd, 1H, J_1 = 8 Hz, J_2 = 10.8 Hz), 7.74–7.78(dd, 1H, J_1 = 8.7 Hz, J_2 = 12.6 Hz), 10.20 (s, 1H).

2.2 Antitumor activities assay in vitro

The antitumor activities of the target compounds (CH01-CH11) were evaluated with human alveolar adenocarinoma cell line A549 and human lung cancer cell line H460 by the standard MTT assay in vitro [12], with gefitinib as the positive control. The cancer cell lines were cultured in minimum essential medium (MEM) supplemented with 10% fetal bovine serum (FBS). Approximately 4×103 cells, suspended in MEM, were plated onto each well of a 96-well plate and incubated in 5% CO₂ at 37 °C for 24 h. The tested compounds at the indicated final concentrations were added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at the terminal concentration of 5 µg/mL and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 µL DMSO each well, and the absorbency at 492 nm (for absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured using the ELISA reader. All of the compounds were tested twice in each of the cell lines. The results expressed as IC₅₀ (inhibitory concentration 50%) were the averages of two measurements and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

3 Result and discussion

3.1 Chemistry

In general, the target compounds (CH01-CH11) were syn-

thesized in satisfactory yields, and the synthetic pathways are described in Scheme 1. The 3-(arylthio)propanoic acid (3) derivatives were synthesized from substituted thiophenol (1) and 3-chloropropanoic acid (2). Subsequently the key intermediate thiochroman-4-ones (4) have been prepared by Friedel-Crafts intermolecular acylation from 3-(arylthio) propanoic acids with yields from 66% to 80% according to the literature method [10]. Meanwhile, methyl carbamimidothioate (6) was synthesized by methylation of thiourea (5)with dimethyl sulfate in 78% yield, and methyl carbamimidothioate (6) was heated with amines under reflux for 2 h to give aminocarboximidamides (7) with yields from 68% to 88% according to the literature method [12]. Finally, a one-pot condensation of thiochroman-4-ones (4) with aminocarboximidamides (7) and aldehydes (8) has provided the target compounds (CH01-CH11) in 45% to 61% yield. All target compounds were unreported in the literature, and characterized by NMR and MS.

3.2 Biological activities

The antitumor activities were determined by the standard MTT assay against two cancer cell lines A549 and H460 with gefitinib, a standard anticancer drug, as the positive control. The screening results expressed as IC_{50} are summarized in Table 1. The IC_{50} values were the average of two independent experiments.

According to the antitumor activity data, some of the target compounds exhibited potential anticancer activities. For example, the target compound **CH05** showed the highest potency against A549 and H460 cancer cell lines while compounds **CH11** and **CH08** were nearly as active as gefitinib against A549 and H460 cancer cell lines. In all tested compounds, **CH10** was inactive. As shown in Table 1, the target compound **CH02** was more potent against H460 cancer cell line than against A549 cancer cell line. These results suggest the series of the target compounds possessed selectivity for A549 cancer cell line.





	IC ₅₀ (μM)			IC ₅₀ (µM)	
	A549	H460		A549	H460
CH01	6.15	17.06	СН07	5.01	8.65
СН02	5.12	1.04	CH08	0.68	2.66
СН03	6.18	8.95	СН09	4.14	3.11
СН04	0.20	4.90	CH10	37.26	88.00
СН05	0.44	3.07	CH11	0.78	4.76
CH06	13.00	12.20	Gefitinib	0.89	16.81

 Table 1
 The antitumor activities of the target compounds

From the above results, some interesting structure-activity relationships can be disclosed that: (i) the substituted position of the methoxy group has no evident effect on the anti-tumor activity. (ii) The introduction of aminocarboximidamides was crucial for improving their activity and selectivity. (iii) The substitution pattern of scaffolds had substantial impact on their potency. Generally, the presence of a number of fluoro groups appears to be a fundamental requirement to obtain potent and selective anti-tumor agents. (iv) The replacement of the substituted phenyl ring with the methoxy group might be detrimental to the activity. All the data suggested that these hybrids might be utilized for the development of new anti-tumor candidates. Especially, the most potent and selective hybrids CH04 and CH05 deserve further evaluation to study their metabolic stability and anti-tumor activities in vivo, and the research results will be reported in due course.

4 Conclusions

In summary, a new series of 4,5-dihydro-1*H*-thiochromeno[4,3-*d*]pyrimidine derivatives were synthesized via the modified method of a one-pot three-component condensation reaction. The antitumor activities of the target compounds were evaluated against two human cancer cell lines (A549 and H460). Most of the target compounds displayed from moderate to excellent antitumor activities against one or two cancer cell lines. In particular, the target compound **CH05** showed potent antitumor activity against both cancer cell lines. Further studies are in progress in our laboratories and will be reported in the future.

This work was supported by the National Natural Science Foundation of China (20474053). The authors would like to thank Analytical and Testing Center, Shenyang Pharmaceutical University for acquiring the NMR spectra data.

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