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Design and synthesis of 3-substituedmethylenethiochroman-4-ones as anticancer agents

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ABSTRACT

A series of 3-substituedmethylenethiochroman-4-ones were designed and synthesized, and their structures were confirmed by ^{1}H NMR, MS, IR, UV and elemental analysis. The evaluation result of their anticancer activity showed that almost all 3-chloromethylenethiochroman-4-ones exhibited high anticancer activity and their activities were all better than reference cisplatin, the IC_{50} of them against cancer cells was at the range of 0.80-9.17 μg/mL. Thus they could be promising candidates for novel anticancer drugs. However, other 3-substituedmethyl- enethiochroman-4-ones had no activity against cancer cells, thus chloromethylene at the 3 position of thiochroman-4-ones was the required active functional group.

KEYWORDS

Anticancer activity;
3-Chloromethylene;
Thiochromanones;
Chlorination;
Synthesis.

INTRODUCTION

Cancer is a global issue and represents a major public health concern, and it is one of the main reasons to result the human death.[1] At present, there are four main tumor therapy ways: chinese medicine therapy, surgical therapy, radiotherapy and chemotherapy.[2,3] Chemotherapy remains the primary means to cure cancer on the point of treatment and applications. Nowadays, there are many anticancer drugs, such as Bleomycin, Carboplatin, Carmustine, Cisplatin, Cyclophosphamide, Fluorouracil, Oxalip- latin, Paclitaxel, Vincristine and so on. But they have some drawbacks such as undesired side effects and multidrug resistance. Therefore it is urgent to look for the new anticancer drugs which have high activity and without or less with side effects. Thiochromanones are of considerable importance as pharmacophoric groups due to their known biological activities. Thiochromanones had been reported to possess important biological activities.[4] Thiochromanone derivatives, such as 3-bromo-4- thiochromanone derivatives,[5] 3-benzyli-enethiochromanone derivatives,[6,7] the Mannich base of thiochromanone derivatives,[8,9] 2,3,3a,4-tetrahydrothiochromeno [4,3-*c*]pyrazole derivatives[10] and 6*H*-thiochromeno[4,3-*b*]- quinolines derivatives[11] *et al* had been synthesized and reported to have antifungal activities. In our study of thiochromanone derivatives as antifungal agents,[10,11] 2-((4-acetylpiperazin-1-yl)me- thylene)-7-chloro-3,4-dihydronaphthalen-1(2*H*)-ones (C in Scheme 1) were designed from the structure of 3-benzylienethiochromanones (A in Scheme 1) and the Mannich base of thiochromanones (B in Scheme 1). However in the synthesis process, (Z)-6-chloro-3-

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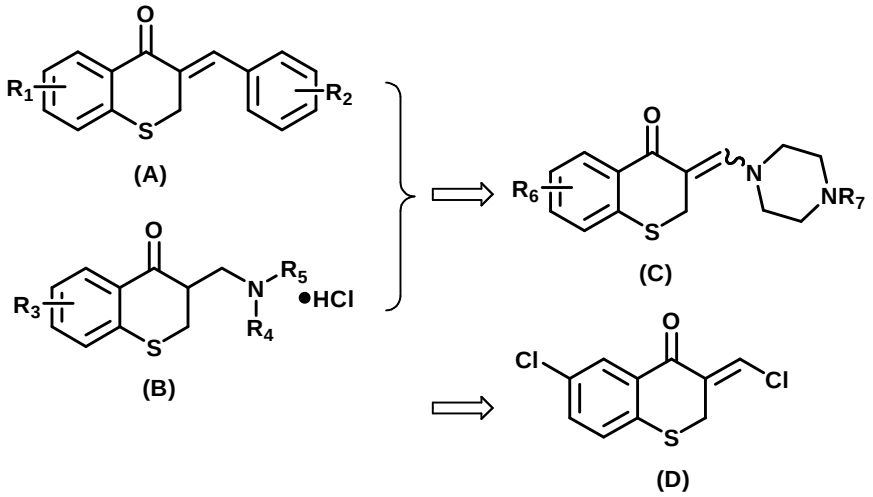
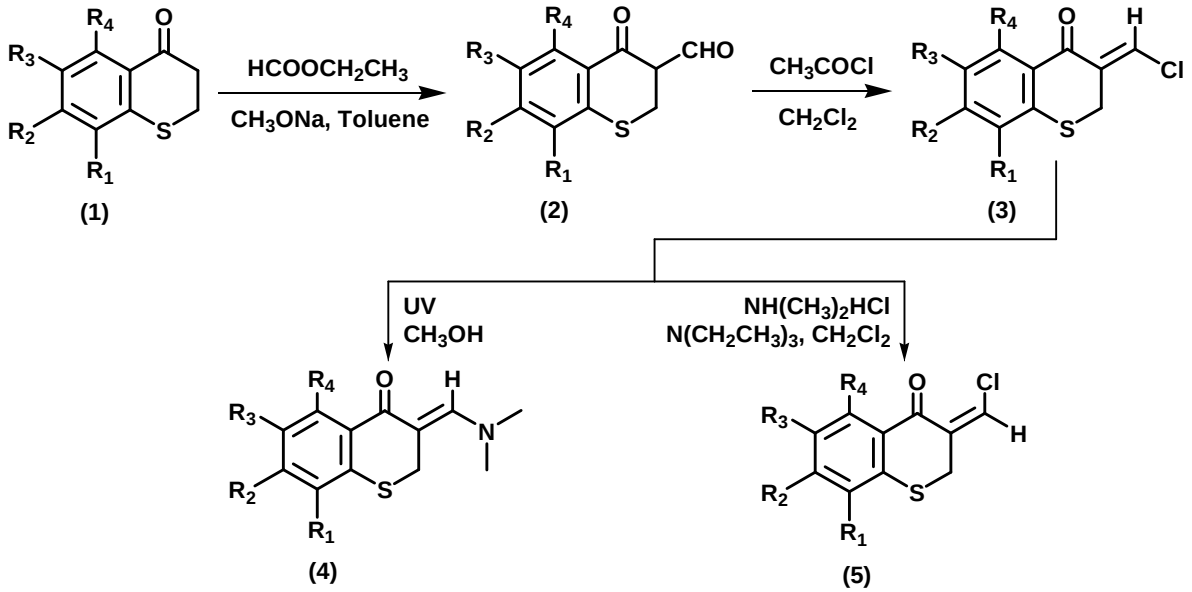
(chloromethylene)thiochroman-4-one (D in Scheme 1) as the byproduct was found to have high antifungal activity.[12] And it was unexpectedly discovered that (Z)-6-chloro-3- chloromethylenethiochroman-4-one had good anticancer activity. So for the aim of getting new anticancer agents, a series of new 3-substituedmethylenethiochroman-4-ones as anticancer agents were designed and synthesized in this paper.



Scheme 1



3a: R_1=Cl, R_2=H, R_3=H_3, R_4=H;
3b: R_1=F, R_2=H, R_3=H, R_4=H;
3c: R_1=CH_3, R_2=H, R_3=H, R_4=H;
3d: R_1=H, R_2=Cl, R_3=Cl, R_4=H;
3e: R_1=CH_3, R_2=H, R_3=CH_3, R_4=H;
3f : R_1=H, R_2=H, R_3=OCH_3, R_4=H;
3g: R_1=Cl, R_2=H, R_3=Cl, R_4=H;
3h: R_1=H, R_2=H, R_3=OH, R_4=H;
4: R_1=Cl, R_2=H, R_3=H, R_4=H;
5: R_1=Cl, R_2=H, R_3=H, R_4=H

Scheme 2 : The synthesis route of targets

EXPERIMENTAL

Materials

Substituted benzenethiols (chemically pure) were from SHOUERFU LLC (ZHEJIANG, China). All other materials were commercially available and used as received unless otherwise noted. Mass spectral data were obtained by LC-MSD XCT Trap G2446A (Agilent Technologies, USA). Melting points were determined SGW X-4 microscopic melting point

(Shanghai Precision & Scientific Instrument Co., Ltd, China). The IR spectra were recorded in potassium bromide on FTIR-8400S (SHIMADZUCORPORATION, Kyoto, Japan). ^{1}H-NMR spectra were recorded in $CDCl_3$ on Bruker Avance III 600Hz spectrometer. The chemical shifts are reported as parts per million (δ ppm) from $(CH_3)_4Si$(TMS) as an internal standard. Elemental analysis was performed on a Carlo Erba-1106 instrument and the results were in acceptable range, 8 cell lines were obtained from military academy of medical sciences (China), Dulbecco's modified Eagle's medium (DMEM) and PRMI 1640 medium, new-bovine serum, fetal bovine serum (FBS), and the other materials for culturing of cells were purchased from Bejing Solarbio Science & Technology Co. Ltd.

Synthesis

General procedure for the synthesis of compounds 1

Compounds **(1)** were synthesized according to published procedures.[12,13]

General procedure for the synthesis of compounds 2

Sodium methoxide (20 mmol) and ethyl formate (20 mmol) were dissolved in the 50 mL of toluene, then a solution of compound **(1)** (10 mmol) in 20 mL of toluene were dropwise added over 20 min in ice bath. The mixture was stirred for 12 h at the temperature < 10 °C. The organic phase was extracted twice with 5% NaOH, the combined aqueous phase was adjusted to pH=2 with HCl, maintaining the temperature at < 5 °C, the solid precipitated was filtered, abundantly washed with water, then air dried. The crude product was recrystallized from 95% (v/v) EtOH to afford the compound **(2a-2h)**.

General procedure for the synthesis of compounds 3

Compound **(2)** (10 mmol) and acetyl chloride (15 mmol) were dissolved in 40mL of dichloromethane in a sealed tube, and the mixture was stirred at 60 °C for 2 h. After the solution was extracted with 0.5 mol/L Na_2CO_3 (15 mL×2), the organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo to give the crude product. The crude product was purified by silica-gel column chromatography (dichloromethane: petroleum ether=1:10(v/v).) to afford the compound **(3)**.

(Z)-8-Chloro-3-(chloromethylene)thiochroman-4-one (3a)

Yellow solid, yield 70%, m. p. 106-109 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), δ: 8.12 (dd, J=7.94, 1.35 Hz, 1H, Ar-H), 7.55 (dd, J=7.81, 1.30 Hz, 1H, Ar-H), 7.38 (s, 1H, C=CH), 7.22 (t, J=7.89 Hz, 1H, Ar-H), 4.06 (s, 2H, SCH_2). IR (KBr): 1660 (C=O), 1579 (C=C) cm^{-1}. MS (APCI), *m/z*: 244.9[M+H]$^+$, 246.9[M+2+H]$^+$. Elemental anal.(%), calcd. for $C_{10}H_6Cl_2OS$: C 49.00, H 2.47, S 13.08; found: C 48.93, H 2.41, S 13.13. UV-vis (MeOH) λ_{max}: 254 nm.

(Z)-3-(Chloromethylene)-8-fluorothiochroman-4-one (3b)

Yellow solid, yield 76%, m. p. 69-72 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), *δ*: 8.12 (dd, *J*=7.94, 1.35 Hz, 1H, Ar-H), 7.55 (dd, *J*=7.81, 1.30 Hz, 1H, Ar-H), 7.38 (s, 1H, C=CH-), 7.22 (t, *J*=7.89 Hz, 1H, Ar-H), 4.06 (s, 2H, SCH_2). IR (KBr): 1670 (C=O), 1589 (C=C) cm^{-1}. MS (APCI), *m/z*: 228.8[M+H]$^+$, 230.8[M+2+H]$^+$. Elemental anal.(%), calcd. for $C_{10}H_6FOS$: C 52.52, H 2.64, S 14.02; found: C 52.46, H 2.56, S 14.08. UV-vis (MeOH) λ_{max}: 241 nm.

(Z)-3-(Chloromethylene)-8-methylthiochroman-4-one (3c)

Yellow solid, yield 55%, m. p. 65-67 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), *δ*: 8.05 (d, *J*=7.88 Hz, 1H, Ar-H), 7.35 (s, 1H, C=CH-), 7.34 (d, *J*=7.56 Hz, 1H, Ar-H), 7.18 (t, *J*=7.65 Hz, 1H, Ar-H), 4.03 (s, 2H, SCH_2), 2.36 (s, 3H, CH_3). IR (KBr): 1654 (C=O), 1589 (C=C) cm^{-1}. MS (APCI), *m/z*: 224.8[M+H]$^+$, 226.8[M+2+H]$^+$. Elemental anal.(%), calcd. for $C_{11}H_9ClOS$: C 58.80, H 4.04, S 14.27; found: C 58.75, H 4.00, S 14.20. UV-vis (MeOH) λ_{max}: 248 nm.

(Z)-6,7-Dichloro-3-(chloromethylene)thiochroman-4-one (3d)

Yellow solid, yield 67%, m. p. 123-124 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), *δ*: 7.63 (d, *J*=2.94 Hz, 1H, Ar-H), 7.36 (s, 1H, C=CH-),7.23 (d, *J*=8.64 Hz, 1H, Ar-H), 7.03 (dd, *J*=8.64, 2.94 Hz, 1H, Ar-H), 4.00 (s, 2H, SCH_2), 3.84 (s, 3H, CH_3). IR (KBr): 1660 (C=O), 1571 (C=C) cm^{-1}. MS (APCI), *m/z*: 278.8 [M+H]$^+$, 280.8[M+2+H]$^+$, 282.8[M+4+H]$^+$. Elemental

anal.(%), calcd. for $C_{10}H_5Cl_3OS$: C 42.96, H 1.80, S 11.47; found: C 42.90, H 1.84, S 11.43. UV-vis (MeOH) λ_{max}: 254 nm.

(Z)-3-(Chloromethylene)-6,8-dimethylthiochroman-4-one (3e)

Yellow solid, yield 65%, m. p. 87-91 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), δ: 7.86 (s, 1H, Ar-H), 7.34 (s, 1H, C=CH-), 7.18 (s, 1H, Ar-H), 4.00 (s, 2H, SCH_2), 2.34 (d, *J*=9.44 Hz, 6H, CH_3). IR (KBr): 1672 (C=O), 1585 (C=C) cm^{-1}. MS (APCI), *m/z*: 238.8 $[M+H]^+$, 240.8$[M+2+H]^+$. Elemental anal.(%), calcd. for $C_{12}H_{11}ClOS$: C 60.37, H 4.64, S 13.43; found: C 60.30, H 4.60; S 13.49. UV-vis (MeOH) λ_{max}: 251 nm.

(Z)-3-(Chloromethylene)-6-methoxythiochroman-4-one (3f)

Yellow solid, yield 81%, m. p. 63-64 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), *δ*: 7.63 (d, *J*=2.94 Hz, 1H, Ar-H), 7.36 (s, 1H, C=CH-), 7.23 (d, *J*=8.64 Hz, 1H, Ar-H), 7.03 (dd, *J*=8.64, 2.94 Hz, 1H, Ar-H), 4.00 (s, 2H, SCH_2), 3.84 (s, 3H, CH_3). IR (KBr): 1652 (C=O), 1589 (C=C) cm^{-1}. MS (APCI), *m/z*: 240.8$[M+H]^+$, 242.8$[M+2+H]^+$. Elemental anal.(%), calcd. for $C_{11}H_9ClO_2S$: C 54.89, H 3.77, S 13.32; found: C 54.75, H 3.69, S 13.28. UV-vis (MeOH) λ_{max}: 238 nm.

(Z)-6,8-Dichloro-3-(chloromethylene)thiochroman-4-one (3g)

Yellow solid, yield 66%, m. p. 129-133 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), *δ*: 8.08 (d, *J*=2.28 Hz, 1H, Ar-H), 7.55 (d, *J*=2.28 Hz, 1H, Ar-H), 7.41 (s, 1H, C=CH-), 4.05 (s, 2H, SCH_2). IR (KBr): 1670 (C=O), 1585 (C=C) cm^{-1}. MS (APCI), *m/z*: 278.8$[M+H]^+$, 280.8$[M+2+H]^+$. Elemental anal.(%), calcd. for $C_{10}H_5Cl_3OS$: C 42.96, H 1.80, S 11.47; found: C 42.90, H 1.85, S 11.40. UV-vis (MeOH) λ_{max}: 252 nm.

(Z)-3-(Chloromethylene)-6-hydroxythiochroman-4-one (3h)

Orange solid, yield 68%, m. p. 162-164 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), *δ*: 7.66 (d, *J*=2.86 Hz, 1H, Ar-H), 7.22 (d, *J*=8.50 Hz, 1H, Ar-H), 7.00 (dd, *J*=8.51, 2.87 Hz, 1H, Ar-H), 7.37 (s, 1H, C=CH-), 5.58 (s, 1H, OH), 4.00 (d, *J* = 0.74 Hz, 2H, SCH_2). IR (KBr): 1652 (C=O), 1581 (C=C) cm^{-1}. MS (APCI), *m/z*: 226.9$[M+H]^+$, 228.9 $[M+2+H]^+$. Elemental anal.(%), calcd. for $C_{11}H_8ClFOS$: C 52.99, H 3.11 S, 14.15; found: C 53.06, H 3.18, S 14.56. UV-vis (MeOH) λ_{max}: 245 nm.

General procedure for the synthesis of compounds 4

Compound **(3)** (5.0 mmol) was dissolved in 60 mL of methanol in a 150 mL of round bottomed flaskirradiating 20 h under 60W UV lamp, solvent was evaporated in vacuo to give the crude product. The crude product was purified by silica-gel column chromatography (dichloromethane: petroleum ether=1:10(v/v).) to afford the compound **(4)**.

(E)-8-Chloro-3-(chloromethylene)thiochroman-4-one (4)

Yellow solid, yield 30%, m. p. 91-93 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), *δ*: 8.16 (dd, *J* = 8.00, 1.29 Hz, 1H, Ar-H), 7.52 (dd, *J*=7.78, 1.31 Hz, 1H, Ar-H), 7.21 (t, *J*=7.89 Hz, Ar-H), 6.73 (s, 1H, C=CH-), 3.86 (s, 2H, SCH_2). IR (KBr): 1670 (C=O), 1593 (C=C) cm^{-1}. MS (APCI), *m/z*: 244.9 $[M+H]^+$, 246.9$[M+2+H]^+$. Elemental anal.(%), calcd. for $C_{10}H_6Cl_2OS$: C 49.00, H 2.47, S 13.08; found: C 48.96, H 2.42, S 13.12. UV-vis (MeOH) λ_{max}: 250 nm.

General procedure for the synthesis of compounds 5

$NH(CH_3)_2$·HCl (6.0 mmol) and $N(CH_2CH_3)_3$ (15.0 mmol) were dissolved in 25 mL of CH_2Cl_2 and cooled to 0 °C, then a solution of compound **(3)** (5.0 mmol) in 5 mL of CH_2Cl_2 were added, dropwise, and the mixture was stirred at 0 °C for 2.5 h. After the solution was extracted with water (20 mL×2), the organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo to give the crude product. The crude product was recrystallized from 95% (v/v) EtOH to afford the compound **(5)**.

(Z)-8-Chloro-3-((dimethylamino)methylene) thiochroman-4-one (5)

Yellow solid, yield 87%, m. p. 123-125 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), *δ*: 8.04 (dd, *J*=7.87, 1.23 Hz, 1H, Ar-H), 7.60 (s, 1H, C=CH-), 7.40 (dd, *J*=7.84, 1.12 Hz, 1H, Ar-H), 7.14 (t, *J*=7.86 Hz, 1H, Ar-H), 4.03 (s, 2H, SCH_2), 3.18 (s, 6H, $C(CH_3)_2$). IR (KBr): 1637 (C=O), 1579(C=C) cm^{-1}. MS (APCI), *m/z*: 253.9$[M+H]^+$. Elemental anal.(%), calcd. for $C_{12}H_{12}ClNOS$: C 56.80, H 4.77, N 5.52, S 12.64;

found: C 56.83, H 4.80, N 5.47, S 12.60. UV-vis (MeOH) λ_{max}: 248 nm.

Tests of anticancer activity

The anticancer activities of target compounds were evaluated *in vitro* on human gastric cancer cells SGC-7901 and BGC-823, human cervical cancer cells Hela, human lung cancer cells A-549, human fibrosarcoma cells HT1080, human breast cells MCF-7, human hepatocellular carcinoma cells HepG2, human colorectal cells LS174T by measuring cell viability according to the MTT method described in the literature[14,15] with cisplatin as the positive control. The cells were seeded in RPMI 1640 medium or DMEM medium (100 μL) in a 96-well plate at a concentration of 4000-5000 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. IC50 values were determined as the drug and sample concentration at 50% inhibition of the cell growth.

RESULTS AND DISCUSSION

Structure elucidation

The structures of the target compounds synthesized were established by mass spectroscopy, elemental analysis, ^{1}H-NMR spectral data and NOE spectral data. The configuration of compounds **(3a)** and **(4)** were assigned by their ^{1}H NMR spectra and ^{1}H-^{1}H NOE spectra.

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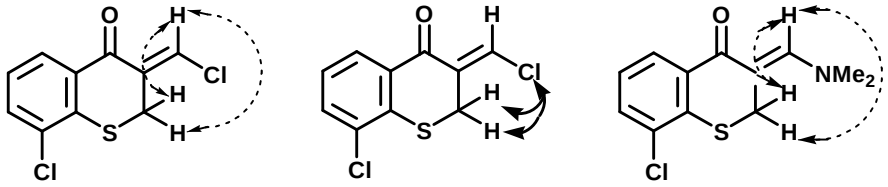

Figure 1 : NOE correlations are shown by arrows

During the synthesis of compound **(5)**, only one product was obtained in the reaction. In order to determine its structure, NOE spectra was also studied. The ^{1}H NMR spectrum of compound **(5)** revealed three singlet signals at δ 3.18, 4.03 and 7.60 characteristic for H of -$N(CH_3)_2$, H of -SCH_2- and H of -C=CHCl, respectively. NOE correlations were observed from H of -C=CHCl to H of -SCH_2-, but there was no correlation from H of -C=CHCl to H of -SCH_2-, as shown in Figure 1. These NOE's confirm the absolute *Z*-configuration of structure 5 (see Figure 2).

Study for anticancer activity

To evaluate the bioactivity of the compounds, we conducted anticancer activity experiments *in vitro*. The anticancer activities of all the target compounds were shown in TABLE 1.

From the TABLE 1 it was found that all the compounds having the functional group of chloromethylene showed high anticancer activity, and the IC50 of them against tested cancer cells was at the range of 0.80-9.17 μg/mL, furthermore their activities were higher than cisplatin. The IC50 of compounds **(3h)** against A-549 was 0.93 μg/mL, furthermore the IC50 of compounds **(3b)** and **(3g)** against SGC7901 were 0.80 and 0.88 μg/mL respectively.

In order to determine chloromethylene at 3 posi-

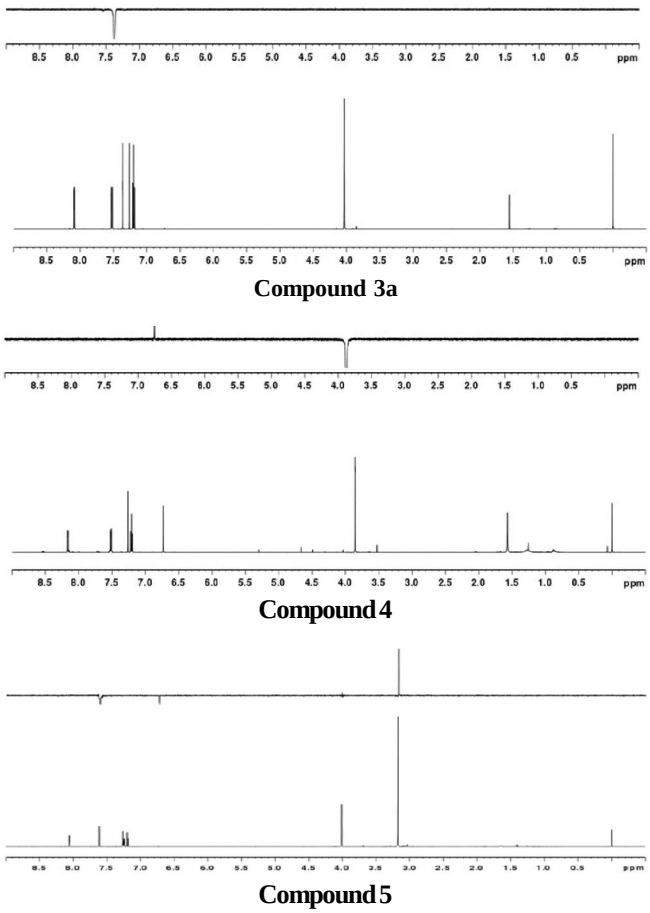

Figure 2 : ^{1}H NMR spectral and NOE spectral of 3a, 4, and 5

tion of compound **(3)** as the active groups, structure optimization of compound **(3a)** were operated. Firstly, compound **(4)** as *E*-isomers of 3a was prepared, but the result of anticancer activity indicated that there was no apparent difference between 3a and 4. Secondly, when chloromethylene was replaced with (dimethylamino)methylene respectively, compound **(5)** were synthesized. The tested result showed that these three compounds had no anticancer activity.

CONCLUSION

From the above, it could be concluded that 3-(chloromethylene)thiochroman- 4-ones as anticancer agents were high active. Different substituents on benzene ring had no obvious influence on the anticancer of 3-(chloromethylene) derivatives, and the anticancer activity of its *Z*/*E* isomer also had little difference, moreover chloromethylene at the 3 position of thiochroman-4-ones was proved to be the major active functional group. Although the exact action mechanism of these compounds against cancer cells needs further study, they can be new potential anticancer agents.

TABLE 1 : *In vitro* anticancer activities of the target compounds

	IC50 (μg/mL)				IC50 (μg/mL)			
	A549	**BGC-823**	**Hela**	**MCF-7**	**SGC7901**	**HepG2**	**LS174T**	**HT1080**
3a	2.91	5.00	4.00	3.46	2.46	4.15	2.96	5.58
3b	1.27	2.51	3.38	3.56	0.80	3.93	2.04	3.67
3c	3.12	2.48	3.72	3.65	2.37	3.23	1.41	2.59
3d	4.49	9.71	6.00	4.51	7.31	7.07	1.42	3.88
3e	2.55	2.59	3.45	2.72	2.07	4.19	1.15	2.92
3f	2.93	2.63	1.61	4.39	2.35	2.72	3.41	3.29
3g	5.53	4.03	4.79	6.64	0.88	6.79	1.32	3.14
3h	0.93	2.63	3.51	3.30	1.64	3.26	1.76	3.10
4	1.95	3.60	2.51	3.43	2.57	2.29	2.75	4.10
5	--	--	--	--	--	--	--	--
Cisplatin	30.00	12.11	8.78	11.01	9.76	30.78	20.09	30.98

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