三唑类白杨素衍生物的设计、合成及其抗增殖活性研究

栾天^{a,b,c} 全哲山^b 方应权^a 杨宏静^{*,a}^(a) 重庆三峡医药高等专科学校药学院 重庆 404120)^(b) 延边大学药学院 吉林延吉 133002)^(c) 沈阳医学院药学院 沈阳 110034)

摘要 合成了 2 个系列的白杨素衍生物, 采用噻唑蓝(MTT)法测试了所有化合物针对六种肿瘤细胞的体外抗增殖活性, 包括 MGC-803, BEL-7402, HepG2, HeLa, A549 以及 SGC-7901 细胞. 实验结果显示, 7-[1-(3-氟苯基)-1*H*-1,2,3-三唑-4-甲氧基]-白杨素(**1c**)与 7-[1-(2-氯苯基)-1*H*-1,2,3-三唑-4-甲氧基]-白杨素(**1g**)针对 MGC-803 细胞的活性与先导化合物白杨素及阳性对照药 5-氟尿嘧啶相比显著提高. 因此, 化合物 **1c** 与 **1g** 具有深入研究用以开发抗癌药物的潜能.

关键词 白杨素; 合成; 三唑; 衍生物; 抗增殖

Design, Synthesis and Antiproliferative Activity of Chrysin Derivatives Bearing Triazole Moieties

Luan, Tian^{a,b,c} Quan, Zheshan^b Fang, Yingquan^a Yang, Hongjing^{*,a}^(a) Department of Pharmacy, Chongqing Three Gorges Medical College, Chongqing 404120)^(b) College of Pharmacy, Yanbian University, Yanji, Jilin 133002)^(c) College of Pharmacy, Shenyang Medical College, Shenyang 110034)

Abstract Two series of novel chrysin derivatives were synthesized, and their antiproliferative activity was evaluated against six human cancer cell lines (MGC-803, BEL-7402, HepG2, HeLa, A549, and SGC-7901) using methyl thiazolyl tetrazolium (MTT) assay. Preliminary bioassay results indicated that 7-((1-(3-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-5-hydroxy-2-phenyl-4*H*-chromen-4-one (**1c**) and 7-((1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-5-hydroxy-2-phenyl-4*H*-chromen-4-one (**1g**) exhibited significantly improved antiproliferative activities against the MGC-803 cell line when compared with the parent compound chrysin and the positive control drug 5-fluorouracil. It demonstrates that compounds **1c** and **1g** are potential agents for cancer therapy.

Keywords chrysin; synthesis; triazole; derivatives; antiproliferation

1 Introduction

Chrysin is a flavonoid compound extracted from the *Senmen oroxyli* of the genus *Dictyophora*. It exhibits a wide range of biological activities including antioxidant,^[1] antiviral,^[2] antiallergy,^[3] anti-inflammatory,^[4] antianxiety^[5] and antiproliferative^[6-9] effects. The antiproliferative activities of chrysin and its derivatives have attracted considerable attention in the recent years. Other biochemical properties of chrysin, such as low solubility *in vitro* and low bioavailability *in vivo*, restrict its clinical application.^[10,11] Therefore, the discovery of highly active derivatives via the structural modification of chrysin during the

development of antiproliferative agents is promising.

Triazole fragments are important pharmacophores that display diverse biological functions, especially antiproliferative activities. The introduction of triazole fragments can improve the pharmacokinetic property, and biological activities of the parent compounds.^[12] Many reports have shown that introducing 1,2,3-triazole or 1,2,4-triazole fragments in different natural products can improve their antiproliferative activities. For example, compound **A** (Figure 1) exhibited a significantly improved antiproliferative activity when compared with the parent compound.^[13] Furthermore, Liu *et al.*^[14] reported a series of compounds linked to 1,2,4-triazole, and as the result, compound **B**

* Corresponding author. E-mail: 40278667@qq.com

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Figure 1 Design of target compounds based on the combination principles

showed promising antiproliferative activities against different types of cancer cell lines.

Previous studies showed that the structural modification in the 7 hydroxyl group can improve the bioactivity of chrysin.^[15] In this study, we synthesized two series of novel chrysin derivatives, linking 1,2,3-triazole and 1,2,4-triazole fragments in the 7-OH position. The antiproliferative activity of the target compounds was evaluated on human gastric cancer (MGC-803), human hepatocellular carcinoma (BEL-7402), human liver cancer (HepG2), human cervical cancer (HeLa), human lung cancer (A549), and human gastric cancer (SGC-7901).

2 Results and discussion

2.1 Chemistry

Intermediate **I** was prepared by the nucleophilic substitution

reaction of chrysin with propargyl bromide, and compounds **1a~1h** were obtained by a click reaction of intermediate **I** with different substitutions of 1-(azidomethyl)benzene (yield: 31.3%~41.2%). Intermediate **II** was prepared by the nucleophilic substitution reaction of chrysin with ethyl bromoacetate, and intermediate **III** was generated from intermediate **II** and hydrazine hydrate. Compounds **2a~2k** were products of the reaction of intermediate **III** with different substitutions of aniline at 82 °C. The yields of **2a~2k** were in the range of 10.3%~25.5%.

2.2 Evaluation of the bioactivity

As summarized in Table 1, compounds **1a**, **1b**, **1c**, and **1g** exhibited stronger antiproliferative activities against the MGC-803 cell line than the lead compound chrysin at 100 μmol/L, while compounds **1e**, **1h**, and **2b** showed a considerably higher antiproliferative activity against the BEL-

1a: R=H, **1b:** R=4-F, **1c:** R=3-F, **1d:** R=2-F, **1e:** R=4-Cl, **1f:** R=3-Cl, **1g:** R=2-Cl, **1h:** R=4-CH₃; **2a:** R=H, **2b:** R=4-F, **2c:** R=3-F, **2d:** R=2-F, **2e:** R=4-Cl, **2f:** R=3-Cl, **2g:** R=2-Cl, **2h:** R=3-Br, **2i:** R=4-CH₃, **2j:** R=3-CH₃, **2k:** R=4-OCH₃

Reagents and conditions: (a) propargyl bromide, K₂CO₃, CH₃COCH₃, 57 °C; (b) different substitutions of 1-(azidomethyl)benzene, CuSO₄·5H₂O, sodium ascorbate, *t*-BuOH/H₂O (V:V=1:1), 30 °C; (c) ethyl bromoacetate, K₂CO₃, CH₃COCH₃, 57 °C; (d) N₂H₄·H₂O, CH₃CH₂OH, 78 °C; (e) DMFDMA, CH₃CN, different substitutions of aniline, CH₃COOH, 82 °C

Scheme 1 Synthetic routes of the target compounds

Table 1 Antiproliferative activity of compounds^a

Compd.	Growth inhibition/% at 100 $\mu\text{mol/L}$					
	MGC-803	BEL-7402	HepG-2	HeLa	A549	SGC-7901
1a	66.83 $\pm$ 1.46	33.18 $\pm$ 0.81	14.20 $\pm$ 0.22	31.90 $\pm$ 0.99	44.67 $\pm$ 0.72	19.31 $\pm$ 0.65
1b	52.71 $\pm$ 0.71	44.01 $\pm$ 0.77	11.89 $\pm$ 0.86	24.42 $\pm$ 1.01	41.20 $\pm$ 1.55	47.68 $\pm$ 1.36
1c	52.82 $\pm$ 2.25	3.31 $\pm$ 0.07	1.02 $\pm$ 0.02	16.81 $\pm$ 0.17	27.89 $\pm$ 0.56	7.30 $\pm$ 0.14
1d	41.52 $\pm$ 1.12	31.44 $\pm$ 0.88	4.91 $\pm$ 0.05	24.40 $\pm$ 0.26	27.89 $\pm$ 0.19	12.78 $\pm$ 0.18
1e	33.81 $\pm$ 0.25	98.18 $\pm$ 1.35	6.81 $\pm$ 0.07	6.32 $\pm$ 0.02	33.91 $\pm$ 0.67	12.64 $\pm$ 0.13
1f	10.59 $\pm$ 0.08	12.80 $\pm$ 0.14	7.43 $\pm$ 0.25	16.70 $\pm$ 0.09	43.46 $\pm$ 0.22	20.98 $\pm$ 0.15
1g	74.28 $\pm$ 1.68	17.44 $\pm$ 0.12	33.02 $\pm$ 0.26	35.07 $\pm$ 0.18	50.71 $\pm$ 0.87	45.64 $\pm$ 0.88
1h	78.33 $\pm$ 0.36	97.60 $\pm$ 0.98	12.92 $\pm$ 0.11	4.11 $\pm$ 0.17	29.13 $\pm$ 0.14	6.44 $\pm$ 0.12
2a	27.33 $\pm$ 0.11	57.24 $\pm$ 0.76	34.01 $\pm$ 0.33	27.30 $\pm$ 0.05	39.49 $\pm$ 0.17	51.71 $\pm$ 1.00
2b	44.51 $\pm$ 0.57	78.26 $\pm$ 1.77	5.11 $\pm$ 0.02	26.81 $\pm$ 0.18	9.01 $\pm$ 0.07	6.81 $\pm$ 0.05
2c	10.72 $\pm$ 0.12	70.70 $\pm$ 1.02	4.52 $\pm$ 0.12	26.42 $\pm$ 0.26	15.01 $\pm$ 0.07	8.22 $\pm$ 0.12
2d	34.62 $\pm$ 0.23	15.49 $\pm$ 0.11	88.40 $\pm$ 1.66	29.33 $\pm$ 0.20	44.11 $\pm$ 0.31	49.22 $\pm$ 0.32
2e	25.21 $\pm$ 0.21	32.30 $\pm$ 0.33	7.50 $\pm$ 0.08	35.41 $\pm$ 0.37	31.11 $\pm$ 0.33	19.70 $\pm$ 0.26
2f	22.62 $\pm$ 0.24	44.33 $\pm$ 0.08	15.62 $\pm$ 0.12	40.92 $\pm$ 0.40	37.80 $\pm$ 0.08	37.71 $\pm$ 0.37
2g	31.71 $\pm$ 0.15	19.01 $\pm$ 0.12	31.02 $\pm$ 0.24	20.10 $\pm$ 0.20	27.90 $\pm$ 0.13	18.41 $\pm$ 0.10
2h	16.80 $\pm$ 0.10	35.71 $\pm$ 0.11	38.79 $\pm$ 0.31	46.50 $\pm$ 0.40	43.01 $\pm$ 0.23	47.83 $\pm$ 0.32
2i	42.11 $\pm$ 0.34	49.81 $\pm$ 0.37	38.82 $\pm$ 0.21	35.51 $\pm$ 0.13	30.11 $\pm$ 0.13	51.09 $\pm$ 0.05
2j	36.89 $\pm$ 0.33	57.64 $\pm$ 0.32	51.60 $\pm$ 0.22	30.49 $\pm$ 0.61	46.02 $\pm$ 0.64	47.11 $\pm$ 0.69
2k	21.73 $\pm$ 0.27	29.44 $\pm$ 0.04	58.11 $\pm$ 0.97	38.22 $\pm$ 0.22	44.52 $\pm$ 0.12	36.54 $\pm$ 0.20
Chrysin	50.89 $\pm$ 0.50	73.02 $\pm$ 0.23	39.33 $\pm$ 0.22	62.89 $\pm$ 0.33	8.80 $\pm$ 0.04	16.30 $\pm$ 0.13

^a Growth inhibitions are presented as the mean $\pm$ SD (standard error of the mean) from three separated experiment.

7402 cell line. However, most compounds lost their antiproliferative activity at lower concentrations and only four compounds had an IC_{50} value ($<100 \mu\text{mol/L}$) lower than that of chrysin against the MGC-803 cell line.

As listed in Table 2, only compounds **1a**, **1b**, **1c** and **1g** exhibited higher antiproliferative activities, indicating that the antiproliferative activity induced by introducing 1,2,3-triazole in the 7-hydroxyl group of chrysin was better than that induced by the introduction of 1,2,4-triazole. Among them, compounds **1c** and **1g** exhibited significant antiproliferative potency against the MGC-803 cell line with IC_{50} values of (18.4 ± 0.14) and (5.92 ± 0.02) $\mu\text{mol/L}$, respectively, which were even better than that of 5-fluorouracil (5-FU). Compound **1g**, with a chlorine atom introduced at the *ortho* position of the benzene ring, had the strongest antiproliferative activity among all target compounds, and improved potency up to two digits $\mu\text{mol/L}$ compared with that of chrysin. It is possible that the chlorine atom acts as a hydrogen bond acceptor and binds to some key proteins involved in cancer cell metabolism, inhibiting their expression. Compound **1g** was 5.2-folds more active than

Table 2 IC_{50} values ($\mu\text{mol/L}$) of several active compounds

Compd.	IC_{50} against MGC-803 cell lines/ $(\mu\text{mol} \cdot \text{L}^{-1})$
1a	26.79 $\pm$ 0.03
1b	95.58 $\pm$ 0.07
1c	18.40 $\pm$ 0.14
1g	5.92 $\pm$ 0.02
Chrysin	>100
5-FU	30.52 $\pm$ 0.36

IC_{50} : concentration that inhibits 50% of cell growth. The values are presented as the mean $\pm$ SD (standard error of the mean) from three separated experiments.

5-FU, which demonstrated that it may be a valuable candidate for further studies.

3 Conclusions

In summary, 19 novel chrysin derivatives were synthesized and their chemical structures were characterized via ^1H NMR, ^{13}C NMR, IR and mass spectra. Biological assays revealed that the introduction of 1,2,3-triazole fragments in the 7-hydroxyl group of chrysin could improve its antiproliferative activity against MGC-803 cell lines. These results are useful for research on more potent novel antiproliferative compounds and further studies are ongoing.

4 Experimental section

All reactions were monitored by thin-layer chromatography (TLC) performed on silica gel plates. IR spectra were recorded (in KBr) on an IR Prestige-21. ^1H NMR and ^{13}C NMR spectra were recorded on an AV-300 spectrometers (Bruker BioSpin, Switzerland) at room temperature, tetramethylsilane (TMS) was used as the internal standard. Mass spectra were measured using a matrix-assisted laser desorption/ionization (MALDI)-time of flight (TOF)/TOF mass spectrometer (Bruker Daltonik, Germany). The major chemicals were purchased from Aldrich Chemical Corporation (Milwaukee, WI). High-resolution mass spectra were recorded using a Thermo Scientific LTQ Orbitrap XL in the electrospray ionisation (ESI) mode. All other chemicals were analytical grade.

3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT) was purchased from Sigma Chemical Co. (St. Louis, MO). All cells were initially purchased from

American Type Culture Collection (ATCC, Manassas, VA, USA). Dulbecco's modified Eagle's medium (DMEM), RPMI-1640 media, and foetal bovine serum (FBS) were provided from Gibco Company (Grand Island, NY, USA). The cells were maintained in RPMI-1640 or DMEM, supplemented with 10% FBS, 100 mg/mL streptomycin and 100 IU/mL penicillin (Grand Island, NY, USA), and at 37 °C in a humidified atmosphere containing 5% CO₂.

4.1 General procedure for the syntheses of intermediates I, II, and III

5-Hydroxy-2-phenyl-7-(prop-2-ynoxy)-4H-chromen-4-one (**I**) and 2-(5-hydroxy-4-oxo-2-phenyl-4H-chromen-7-yloxy)acetohydrazide (**III**) were synthesized as per the protocol described in a previous study.^[16,17]

Chrysin (1.27 g, 5.0 mmol), K₂CO₃ (1.00 g, 7.5 mmol) and ethyl bromoacetate (1.00 g, 6.0 mmol) were added to CH₃COCH₃ (50 mL). The mixture was stirred at 57 °C for 2 h. Then, the solvent was evaporated *in vacuo*, water was added (20 mL), the mixture was filtered, and the residue was washed with water to obtain ethyl 2-(5-hydroxy-4-oxo-2-phenyl-4H-chromen-7-yloxy)acetate (**II**).^[18] ¹H NMR (CDCl₃, 300 MHz) δ: 12.83 (s, 1H), 8.11 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.68~7.53 (m, 3H), 7.08 (s, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 4.97 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).

4.2 General procedure for the syntheses of compounds 1a~1h

A mixture of compound **I** (146 mg, 0.5 mmol), different substitutions of 1-(azidomethyl)benzene (0.5 mmol), CuSO₄·5H₂O (10 mg, 0.05 mmol) and sodium ascorbate (17 mg, 0.1 mmol) were added to *t*-BuOH/H₂O (*V*: *V* = 1:1, 30 mL) and stirred at 30 °C for 12 h. After confirming the reaction progress by TLC, *t*-BuOH was evaporated *in vacuo*. Then, the mixture was extracted with dichloromethane (10 mL×3) and washed with saline (10 mL). Finally, the mixture was purified using silica gel column chromatography and eluted with dichloromethane/methanol (*V*: *V* = 100:1) to obtain the target compounds **1a**~**1h**.

5-Hydroxy-2-phenyl-7-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-4H-chromen-4-one (**1a**): Pale yellow solid, yield 41.2%. m.p. 186~187 °C; ¹H NMR (CDCl₃, 300 MHz) δ: 12.72 (s, 1H, OH), 7.88 (d, *J* = 5.9 Hz, 2H, ArH), 7.57~7.52 (m, 4H, ArH), 7.40~7.37 (m, 3H, ArH), 7.31~7.26 (m, 2H, ArH), 6.67 (s, 1H, ArH), 6.61 (d, *J* = 2.0 Hz, 1H, ArH), 6.41 (d, *J* = 2.0 Hz, 1H, ArH), 5.55 (s, 2H, CH₂), 5.26 (s, 2H, CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ: 182.50, 164.13, 164.03, 162.15, 157.77, 134.28, 133.18, 131.92, 131.21, 129.22 (2C), 129.11 (2C), 128.95, 128.20 (2C), 126.34 (2C), 122.88, 106.08, 105.92, 99.06, 93.27, 62.42, 54.39; IR (KBr) *v*: 3138, 1660, 1612, 1498, 1446, 1350, 1165 cm⁻¹; MS-MALDI *m/z*: 426 [M+H⁺]; HRMS (ESI) calcd for C₂₅H₂₀N₃O₄ [M+H⁺] 426.1448, found 426.1443.

7-((1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (**1b**): Pale yellow

solid, yield 39.5%. m.p. 171~173 °C; ¹H NMR (CDCl₃, 300 MHz) δ: 12.75 (s, 1H, OH), 7.91 (dd, *J* = 7.7, 1.9 Hz, 2H, ArH), 7.59~7.52 (m, 4H, ArH), 7.34~7.29 (m, 2H, ArH), 7.13~7.07 (m, 2H, ArH), 6.70 (s, 1H, ArH), 6.63 (d, *J* = 2.2 Hz, 1H, ArH), 6.44 (d, *J* = 2.2 Hz, 1H, ArH), 5.55 (s, 2H, CH₂), 5.30 (s, 2H, CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ: 182.50, 164.16, 163.99, 162.90 (d, *J* = 151.5 Hz), 162.16, 157.77, 143.60, 137.79, 131.94, 131.19, 130.10 (d, *J* = 151.5 Hz, 2C), 129.12 (2C), 126.34 (2C), 122.74, 116.26 (d, *J* = 21.8 Hz, 2C), 106.09, 105.92, 99.02, 93.27, 62.38, 53.62; IR (KBr) *v*: 3136, 1662, 1614, 1502, 1452, 1348, 1165 cm⁻¹; MS-MALDI *m/z*: 444 [M+H⁺]; HRMS (ESI) calcd for C₂₅H₂₀N₃O₄ [M+H⁺] 444.1354, found 444.1354.

7-((1-(3-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (**1c**): Pale yellow solid, yield 33.5%. m.p. 175~177 °C; ¹H NMR (CDCl₃, 300 MHz) δ: 12.75 (s, 1H, OH), 7.91 (dd, *J* = 7.7, 1.8 Hz, 2H, ArH), 7.63~7.51 (m, 4H, ArH), 7.38 (dd, *J* = 13.8, 7.9 Hz, 1H, ArH), 7.11~7.06 (m, 2H, ArH), 7.00 (d, *J* = 9.2 Hz, 1H, ArH), 6.69 (s, 1H, ArH), 6.64 (d, *J* = 2.2 Hz, 1H, ArH), 6.44 (d, *J* = 2.2 Hz, 1H, ArH), 5.57 (s, 2H, CH₂), 5.31 (s, 2H, CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ: 182.51, 168.44 (d, *J* = 132.0 Hz), 164.16, 163.97, 162.15, 157.76, 143.69, 136.64 (d, *J* = 7.5 Hz), 131.95, 131.18, 130.91 (d, *J* = 8.3 Hz), 129.13 (2C), 126.35 (2C), 123.66 (d, *J* = 3.0 Hz), 122.96, 116.00 (d, *J* = 21.0 Hz), 115.13 (d, *J* = 21.8 Hz), 114.98, 105.91, 99.03, 93.26, 62.37, 53.71; IR (KBr) *v*: 3165, 1660, 1612, 1502, 1450, 1359, 1168 cm⁻¹. MS-MALDI *m/z*: 444 [M+H⁺]; HRMS (ESI) calcd for C₂₅H₁₉FN₃O₄ [M+H⁺] 444.1354, found 444.1354.

7-((1-(2-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (**1d**): Pale yellow solid, yield 31.3%. m.p. 201~203 °C; ¹H NMR (CDCl₃, 300 MHz) δ: 12.75 (s, 1H, OH), 7.91 (dd, *J* = 7.6, 1.9 Hz, 2H, ArH), 7.70 (s, 1H, ArH), 7.57~7.54 (m, 3H, ArH), 7.32~7.34 (m, 2H, ArH), 7.21~7.12 (m, 2H, ArH), 6.70 (s, 1H, ArH), 6.65 (d, *J* = 2.2 Hz, 1H, ArH), 6.45 (d, *J* = 2.2 Hz, 1H, ArH), 5.64 (s, 2H, CH₂), 5.28 (s, 2H, CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ: 182.53, 164.15, 164.03, 162.14, 158.86 (d, *J* = 165.0 Hz), 143.44, 131.94, 131.21 (d, *J* = 0.8 Hz), 131.10, 130.75 (d, *J* = 3.0 Hz), 129.13 (2C), 126.35 (2C), 124.97, 124.92, 123.14, 123.12, 118.83 (d, *J* = 19.5 Hz), 115.95 (d, *J* = 21.0 Hz), 106.80, 99.05, 93.27, 62.36, 50.92; IR (KBr) *v*: 3134, 1670, 1614, 1496, 1452, 1350, 1161 cm⁻¹; MS-MALDI *m/z*: 444 [M+H⁺]; HRMS (ESI) calcd for C₂₅H₂₀N₃O₄ [M+H⁺] 444.1354, found 444.1353.

7-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (**1e**): Pale yellow solid, yield 37.2%. m.p. 172~173 °C; ¹H NMR (CDCl₃, 300 MHz) δ: 12.74 (s, 1H, OH), 7.92~7.89 (m, 2H, ArH), 7.60~7.54 (m, 4H, ArH), 7.40~7.37 (m, 2H, ArH), 7.28~7.24 (m, 2H, ArH), 6.69 (s, 1H, ArH), 6.63 (d, *J* = 2.2 Hz, 1H, ArH), 6.43 (d, *J* = 2.2 Hz, 1H, ArH), 5.54 (s, 2H, CH₂), 5.30 (s, 2H, CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ: 182.51, 164.17, 163.98, 162.17, 157.77, 143.69, 135.04,

132.77, 131.95, 131.20, 129.51 (2C), 129.45 (2C), 129.13 (2C), 126.35 (2C), 122.80, 106.10, 105.93, 99.02, 93.28, 62.37, 53.62; IR (KBr) ν : 3128, 1664, 1612, 1496, 1450, 1346, 1161 cm^{-1} ; MS-MALDI m/z : 460 $[\text{M}+\text{H}^+]$; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{19}\text{ClN}_3\text{O}_4$ $[\text{M}+\text{H}^+]$ 460.1058, found 460.1056.

7-((1-(3-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-5-hydroxy-2-phenyl-4*H*-chromen-4-one (**1f**): Pale yellow solid, yield 35.1%. m.p. 152~153 °C; ^1H NMR (CDCl_3 , 300 MHz) δ : 12.74 (s, 1H, OH), 7.91~7.88 (m, 2H, ArH), 7.63~7.54 (m, 4H, ArH), 7.45~7.29 (m, 3H, ArH), 7.19 (d, $J=4.7$ Hz, 1H, ArH), 6.70 (s, 1H, ArH), 6.63 (d, $J=2.2$ Hz, 1H, ArH), 6.44 (d, $J=2.1$ Hz, 1H, ArH), 5.55 (s, 2H, CH_2), 5.29 (s, 2H, CH_2); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 182.52, 164.17, 163.96, 162.14, 157.77, 143.73, 136.20, 135.11, 131.96, 131.16, 130.54, 129.18, 129.13 (2C), 128.20, 126.35 (2C), 126.20, 122.96, 106.09, 105.90, 99.05, 93.26, 62.35, 53.65; IR (KBr) ν : 3072, 1666, 1612, 1498, 1452, 1354, 1165 cm^{-1} ; MS-MALDI m/z : 460 $[\text{M}+\text{H}^+]$; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{19}\text{ClN}_3\text{O}_4$ $[\text{M}+\text{H}^+]$ 460.1059, found 460.1060.

7-((1-(2-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-5-hydroxy-2-phenyl-4*H*-chromen-4-one (**1g**): Pale yellow solid, yield 31.7%. m.p. 146~147 °C; ^1H NMR (CDCl_3 , 300 MHz) δ : 12.75 (s, 1H, OH), 7.92~7.89 (m, 2H, ArH), 7.71 (s, 1H, ArH), 7.56~7.45 (m, 5H, ArH), 7.37~7.30 (m, 2H, ArH), 6.70~6.64 (m, 2H, ArH), 6.45 (d, $J=2.1$ Hz, 1H, ArH), 5.71 (s, 2H, CH_2), 5.29 (s, 2H, CH_2); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 182.52, 164.15, 164.02, 162.13, 157.76, 143.32, 133.61, 132.13, 131.94, 131.19, 130.57, 130.48, 130.04, 129.13 (2C), 127.70, 126.35 (2C), 123.28, 106.08, 105.91, 99.06, 93.30, 62.38, 51.63; IR (KBr) ν : 3143, 1660, 1614, 1498, 1444, 1377, 1159 cm^{-1} ; MS-MALDI m/z : 460 $[\text{M}+\text{H}^+]$; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{19}\text{ClN}_3\text{O}_4$ $[\text{M}+\text{H}^+]$ 460.1059, found 460.1055.

5-Hydroxy-2-phenyl-7-((1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (**1h**): Pale yellow solid, yield 37.8%. m.p. 166~168 °C; ^1H NMR (CDCl_3 , 300 MHz) δ : 12.82 (s, 1H, OH), 8.32 (s, 1H, ArH), 8.10~8.08 (m, 2H, ArH), 7.64~7.56 (m, 3H, ArH), 7.21 (dd, $J=20.2, 8.0$ Hz, 4H, ArH), 7.05 (s, 1H, ArH), 6.94 (d, $J=2.1$ Hz, 1H, ArH), 6.49 (d, $J=2.1$ Hz, 1H, ArH), 5.57 (s, 2H, ArH), 5.28 (s, 2H, ArH), 2.27 (s, 3H, CH_3); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 182.31, 163.93, 161.97, 157.59, 143.30, 138.77, 131.79, 131.16, 131.03, 129.74 (2C), 128.97 (2C), 128.72, 128.13 (2C), 126.18 (2C), 122.76, 105.90, 105.72, 98.92, 93.11, 62.29, 54.04, 21.07; IR (KBr) ν : 3120, 1656, 1620, 1496, 1446, 1377, 1157 cm^{-1} ; MS-MALDI m/z : 440 $[\text{M}+\text{H}^+]$; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}^+]$ 440.1605, found 440.1602.

4.3 General procedure for the syntheses of compounds 2a~2k

Compound **III** (652.0 mg, 2.0 mmol) and *N,N*-dimethyl-formamide dimethyl acetal (DMFDMA, 260.0 mg, 2.2 mmol) were added to CH_3CN (30 mL). The mixture was stirred at 50 °C for 2 h. Then, different substitutions of

aniline (3.0 mmol) and CH_3COOH (0.72 g, 12 mmol) were added, and the mixture was stirred at 82 °C for 12 h. After confirming the reaction progress by TLC, the solvent was evaporated *in vacuo*. The mixture was then purified using silica gel column chromatography and eluted using a gradient of dichloromethane/methanol ($V:V=120:1$) to obtain the target compounds **2a~2k**.

5-Hydroxy-2-phenyl-7-((4-phenyl-4*H*-1,2,4-triazol-3-yl)methoxy)-4*H*-chromen-4-one (**2a**): Pale yellow solid, Yield 23.5%. m.p. 188~189 °C; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ : 12.80 (s, 1H, OH), 8.92 (s, 1H, Triazole-H), 8.07 (d, $J=7.0$ Hz, 2H, ArH), 7.78~7.35 (m, 8H, ArH), 7.03 (s, 1H, ArH), 6.85 (d, $J=1.5$ Hz, 1H, ArH), 6.40 (d, $J=1.5$ Hz, 1H, ArH), 5.38 (s, 2H, CH_2); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ : 187.89, 182.58, 164.07, 163.62, 161.60, 157.58, 149.17, 145.88, 134.02, 132.67, 130.98, 130.27, 129.85, 129.63, 126.92, 125.77, 105.91, 105.85, 99.17, 94.17, 60.48; IR (KBr) ν : 3089, 1666, 1622, 1502, 1450, 1550, 1338, 1153 cm^{-1} ; MS-MALDI m/z : 412 $[\text{M}+\text{H}^+]$; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}^+]$ 412.1292, found 412.1291.

7-((4-(4-Fluorophenyl)-4*H*-1,2,4-triazol-3-yl)methoxy)-5-hydroxy-2-phenyl-4*H*-chromen-4-one (**2b**): Pale yellow solid, yield 24.5%. m.p. 177~179 °C; ^1H NMR (CDCl_3 , 300 MHz) δ : 12.76 (s, 1H, OH), 8.35 (s, 1H, Triazole-H), 7.91 (d, $J=6.0$ Hz, 2H, ArH), 7.57~7.42 (m, 5H, ArH), 7.27 (d, $J=6.0$ Hz, 2H, ArH), 6.70 (s, 2H, ArH), 6.35 (s, 1H, ArH), 5.29 (d, $J=15.5$ Hz, 2H, CH_2); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 182.49, 164.32, 162.92, 162.25, 159.84 (d, $J=135.8$ Hz), 157.76, 149.40, 144.83, 132.04, 131.06, 130.75, 129.29 (d, $J=3.0$ Hz), 129.14 (2C), 127.56 (d, $J=9.0$ Hz, 2C), 126.38 (2C), 117.20 (d, $J=23.3$ Hz, 2C), 106.51, 106.00, 99.04, 93.11, 59.63; IR (KBr) ν : 3068, 1654, 1614, 1512, 1496, 1450, 1338, 1155 cm^{-1} ; MS-MALDI m/z : 430 $[\text{M}+\text{H}^+]$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{17}\text{FN}_3\text{O}_4$ $[\text{M}+\text{H}^+]$ 430.1198, found 430.1197.

7-((4-(3-Fluorophenyl)-4*H*-1,2,4-triazol-3-yl)methoxy)-5-hydroxy-2-phenyl-4*H*-chromen-4-one (**2c**): Pale yellow solid, yield 21.5%. m.p. 174~176 °C; ^1H NMR (CDCl_3 , 300 MHz) δ : 12.76 (s, 1H, OH), 8.39 (s, 1H, Triazole-H), 7.93~7.90 (m, 2H, ArH), 7.55~7.53 (m, 3H, ArH), 7.28~7.25 (m, 4H, ArH), 6.76~6.68 (m, 2H, ArH), 6.37 (d, $J=2.3$ Hz, 1H, ArH), 5.31 (d, $J=4.6$ Hz, 2H, CH_2); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ : 182.57, 164.10, 163.58, 162.54 (d, $J=244.5$ Hz), 161.62, 157.58, 149.11, 145.82, 135.38 (d, $J=10.5$ Hz), 132.67, 132.02 (d, $J=9.0$ Hz), 130.98, 129.62 (2C), 126.92 (2C), 122.03 (d, $J=3.0$ Hz), 116.80 (d, $J=21.0$ Hz), 113.51 (d, $J=24.8$ Hz), 105.94 (2C), 99.16, 94.20, 60.56; IR (KBr) ν : 3066, 1656, 1614, 1512, 1496, 1448, 1340, 1155 cm^{-1} ; MS-MALDI 430 $[\text{M}+\text{H}^+]$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{17}\text{FN}_3\text{O}_4$ $[\text{M}+\text{H}^+]$ 430.1198, found 430.1192.

7-((4-(2-Fluorophenyl)-4*H*-1,2,4-triazol-3-yl)methoxy)-5-hydroxy-2-phenyl-4*H*-chromen-4-one (**2d**): Pale yellow solid, yield 14.5%. m.p. 175~177 °C; ^1H NMR (CDCl_3 , 300 MHz) δ : 12.71 (s, 1H, OH), 8.35 (s, 1H, Triazole-H), 7.90 (dd, $J=7.8, 1.7$ Hz, 2H, ArH), 7.54 (dd, $J=7.2, 3.4$

Hz, 4H, ArH), 7.43~7.33 (m, 3H, ArH), 6.69 (s, 1H, ArH), 6.61 (d, $J=2.2$ Hz, 1H), 6.20 (d, $J=2.2$ Hz, 1H, ArH), 5.33 (d, $J=7.1$ Hz, 2H, CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ : 182.48, 164.28, 162.95, 162.54 (d, $J=133.5$ Hz), 162.09, 157.69, 149.73, 145.04, 141.64, 132.12 (d, $J=8.3$ Hz), 132.03, 131.04, 129.13 (2C), 127.94, 126.37 (2C), 125.32 (d, $J=3.8$ Hz), 117.18 (d, $J=19.5$ Hz), 106.45, 105.95, 99.07, 92.91, 60.27; IR (KBr) ν : 3066, 1654, 1612, 1514, 1496, 1448, 1338, 1157 cm⁻¹; MS-MALDI m/z : 430 [M+H⁺]; HRMS (ESI) calcd for C₂₄H₁₇FN₃O₄ [M+H⁺] 430.1198, found 430.1199.

7-((4-(4-Chlorophenyl)-4H-1,2,4-triazol-3-yl)methoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (**2e**): Pale yellow solid, yield 25.5%. m.p. 166~168 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 12.81 (s, 1H, OH), 8.92 (s, 1H, Triazole-H), 8.08 (d, $J=8.0$ Hz, 2H, ArH), 7.64~7.29 (m, 7H, ArH), 7.04 (s, 1H, ArH), 6.84 (d, $J=2.1$ Hz, 1H, ArH), 6.41 (d, $J=2.1$ Hz, 1H, ArH), 5.41 (s, 2H, CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ : 182.43, 164.26, 162.84, 162.20, 157.69, 149.18, 144.58, 136.30, 131.99, 131.71, 131.00, 130.30 (2C), 129.09 (2C), 126.72 (2C), 126.34 (2C), 106.48, 105.94, 98.99, 93.10, 59.58; IR (KBr) ν : 3107, 1656, 1614, 1504, 1452, 1350, 1159 cm⁻¹. MS-MALDI m/z : 446 [M+H⁺]; HRMS (ESI) calcd for C₂₄H₁₇ClN₃O₄ [M+H⁺] 446.0902, found 446.0907.

7-((2-(3-Chlorophenyl)-2H-1,2,4-triazol-3-yl)methoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (**2f**): Pale yellow solid, yield 22.1%. m.p. 159~160 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 12.75 (s, 1H, OH), 8.36 (s, 1H, Triazole-H), 7.90 (d, $J=8.1$ Hz, 2H, ArH), 7.56~7.46 (m, 6H, ArH), 7.34 (s, 1H, ArH), 6.70 (d, $J=2.6$ Hz, 2H, ArH), 6.35 (d, $J=2.2$ Hz, 1H, ArH), 5.28 (s, 2H, CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ : 182.45, 164.31, 162.34, 144.44, 135.87, 134.39, 131.96, 131.10, 130.33, 129.11 (2C), 126.37 (2C), 125.90, 123.63, 113.03, 106.58, 106.04, 99.10, 93.24, 77.41, 76.99, 76.57, 59.80; IR (KBr) ν : 3111, 1660, 1618, 1502, 1450, 1350, 1157 cm⁻¹; MS-MALDI m/z : 446 [M+H⁺]; HRMS (ESI) calcd for C₂₄H₁₇ClN₃O₄ [M+H⁺] 446.0902, found 446.0905.

7-((4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)methoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (**2g**): Pale yellow solid, yield 10.3%. m.p. 157~158 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 12.67 (s, 1H, OH), 8.31 (s, 1H, Triazole-H), 7.87 (dd, $J=7.8, 1.5$ Hz, 2H, ArH), 7.63~7.60 (m, 1H, ArH), 7.54~7.48 (m, 4H, ArH), 7.46~7.40 (m, 2H, ArH), 6.66 (s, 1H, ArH), 6.57 (d, $J=2.2$ Hz, 1H, ArH), 6.17 (d, $J=2.2$ Hz, 1H, ArH), 5.30 (d, $J=5.3$ Hz, 2H, CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ : 182.44, 164.25, 162.99, 162.03, 157.66, 149.67, 144.91, 132.01, 131.84, 131.50, 131.06, 131.00, 130.78, 129.11 (2C), 128.83, 128.14, 126.35 (2C), 106.38, 105.89, 99.06, 92.86, 60.21; IR (KBr) ν : 3103, 1654, 1618, 1504, 1454, 1346, 1157 cm⁻¹; MS-MALDI m/z : 446 [M+H⁺]; HRMS (ESI) calcd for C₂₄H₁₇ClN₃O₄ [M+H⁺] 446.0902, found 446.0901.

7-((4-(3-Bromophenyl)-4H-1,2,4-triazol-3-yl)methoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one (**2h**): Pale yellow solid, yield 20.8%. m.p. 179~181 °C; ¹H NMR (CDCl₃,

300 MHz) δ : 12.77 (s, 1H, OH), 8.37 (s, 1H, Triazole-H), 7.92 (d, $J=8.2$ Hz, 2H, ArH), 7.70 (d, $J=8.3$ Hz, 1H, ArH), 7.63~7.55 (m, 4H, ArH), 7.48~7.38 (m, 2H, ArH), 6.71 (s, 2H, ArH), 6.38 (d, $J=2.2$ Hz, 1H, ArH), 5.31 (s, 2H, CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ : 182.46, 164.32, 162.91, 162.35, 157.77, 149.18, 144.44, 134.47, 133.27, 131.96, 131.23, 131.15, 129.11 (2C), 128.80, 126.37 (2C), 124.10, 123.49, 106.59, 106.04, 99.11, 93.25, 59.80; IR (KBr) ν : 3107, 1660, 1618, 1500, 1452, 1350, 1157 cm⁻¹; MS-MALDI m/z : 490 [M+H⁺]; HRMS (ESI) calcd for C₂₄H₁₇BrN₃O₄ [M+H⁺] 490.0397, found 490.0393.

5-Hydroxy-2-phenyl-7-((4-*p*-tolyl-4H-1,2,4-triazol-3-yl)methoxy)-4H-chromen-4-one (**2i**): Pale yellow solid, yield 25.4%. m.p. 165~166 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 12.81 (s, 1H, OH), 8.88 (s, 1H, Triazole-H), 8.09~8.06 (m, 2H, ArH), 7.64~7.57 (m, 3H, ArH), 7.41 (dd, $J=28.2, 8.2$ Hz, 4H, ArH), 7.05 (s, 1H, ArH), 6.87 (d, $J=2.1$ Hz, 1H, ArH), 6.43 (d, $J=2.1$ Hz, 1H, ArH), 5.36 (s, 2H, CH₂), 2.35 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ : 182.32, 164.08, 163.02, 161.99, 157.56, 149.23, 144.73, 140.27, 131.88, 130.90, 130.48 (2C), 128.99 (2C), 126.21 (2C), 125.09 (2C), 106.25, 105.76, 98.99, 93.08, 90.29, 59.53, 21.09; IR (KBr) ν : 3115, 1664, 1612, 1517, 1448, 1336, 1155 cm⁻¹; MS-MALDI m/z : 426 [M+H⁺]; HRMS (ESI) calcd for C₂₅H₂₀N₃O₅ [M+H⁺] 426.1448, found 426.1446.

5-Hydroxy-2-phenyl-7-((4-*m*-tolyl-4H-1,2,4-triazol-3-yl)methoxy)-4H-chromen-4-one (**2j**): Pale yellow solid, yield 15.4%. m.p. 175~177 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 12.75 (s, 1H, OH), 8.37 (s, 1H, Triazole-H), 7.93~7.90 (m, 2H, ArH), 7.56 (d, $J=7.3$ Hz, 3H, ArH), 7.46~7.34 (m, 2H, ArH), 7.23 (s, 2H, ArH), 6.72~6.71 (m, 2H, ArH), 6.35 (d, $J=2.2$ Hz, 1H, ArH), 5.28 (s, 2H, CH₂), 2.44 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ : 182.51, 164.29, 163.14, 162.18, 157.75, 153.43, 144.73, 142.39, 140.45, 132.01, 131.09, 130.80, 129.82, 129.13 (2C), 126.38 (2C), 126.01, 122.38, 106.44, 105.97, 99.15, 93.21, 59.69, 21.32; IR (KBr) ν : 3072, 1658, 1618, 1502, 1450, 1350, 1159 cm⁻¹; MS-MALDI m/z : 426 [M+H⁺]; HRMS (ESI) calcd for C₂₅H₂₀N₃O₅ [M+H⁺] 426.1448, found 426.1446.

5-Hydroxy-7-((4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-yl)methoxy)-2-phenyl-4H-chromen-4-one (**2k**): Pale yellow solid, yield 24.9%. m.p. 163~165 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 12.82 (s, 1H, OH), 8.85 (s, 1H, Triazole-H), 8.10~8.07 (m, 2H, ArH), 7.62~7.59 (m, 3H, ArH), 7.50 (d, $J=8.9$ Hz, 2H, ArH), 7.11~7.06 (m, 3H, ArH), 6.87 (d, $J=2.1$ Hz, 1H, ArH), 6.44 (d, $J=2.1$ Hz, 1H, ArH), 5.34 (s, 2H, CH₂), 3.79 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ : 182.31, 164.08, 163.03, 161.99, 160.50, 157.57, 149.43, 144.92, 131.86, 130.90, 128.98 (2C), 126.73 (2C), 126.21 (2C), 125.70, 114.95 (2C), 106.25, 105.77, 98.99, 93.06, 59.52, 55.57; IR (KBr) ν : 3078, 1658, 1616, 1517, 1452, 1348, 1157 cm⁻¹; MS-MALDI 442 [M+H⁺]; HRMS (ESI) calcd for C₂₅H₂₀N₃O₅ [M+H⁺] 442.1398, found 442.1396.

4.4 Biological testing

The antiproliferative activities of the target compounds against MGC-803, BEL-7402, HepG2, HeLa, A549, and SGC-7901 cell lines were evaluated by MTT assay *in vitro*, with 5-FU as the positive control. All cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS). Cells were detached by trypsin, seeded at 9×10^3 cells in a 96-well plate and incubated in 5% CO₂ at 37 °C overnight. Then the cells are treated with the test compounds at different concentrations (1, 10, 50, and 100 μmol/L) and incubated for 48 h. Fresh MTT solutions were added to each well and incubated at 37 °C for 4 h. The MTT-formazan formed by metabolically viable cells was dissolved by dimethyl sulfoxide (DMSO, 150 μL) in each well and monitored by a microplate reader at a wavelength of 492 nm. IC₅₀ was defined as the drug concentrations that inhibited the cell number to 50% after 48 h.

Supporting Information NMR spectra of target compounds. The Supporting Information is available free of charge via the Internet at <http://sioc-journal.cn/>.

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