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BRIEF REPORT

Synthesis, telomerase inhibitory and anticancer activity of new 2-phenyl-4H-chromone derivatives containing 1,3,4-oxadiazole moiety

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ABSTRACT

Based on previous studies, 66 2-phenyl-4H-chromone derivatives containing amide and 1,3,4-oxadiazole moieties were prepared as potential telomerase inhibitors. The results showed most of the title compounds exhibited significantly inhibitory activity on telomerase. Among them, some compounds demonstrated the most potent telomerase inhibitory activity ($IC_{50} < 1\,\mu M$), which was significantly superior to the staurosporine ($IC_{50} = 6.41\,\mu M$). In addition, clear structure–activity relationships were summarised, indicating that the substitution of the methoxy group and the position, type and number of the substituents on the phenyl ring had significant effects on telomerase activity. Among them, compound **A33** showed considerable inhibition against telomerase. Flow cytometric analysis showed that compound **A33** could arrest MGC-803 cell cycle at G2/M phase and induce apoptosis in a concentration-dependent way. Meanwhile, Western blotting revealed that this compound could reduce the expression of dyskerin, which is a fragment of telomerase.

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2-phenyl-4H-chromone; synthesis; telomerase inhibitor; anticancer activity; dyskerin

1. Introduction

Telomerase is a ribonucleoprotein that exists in mammalian cells, playing an important role in maintaining the length of stable telomere and the chromosomal integrity of frequently dividing cells[1]. It is almost undetectable in most somatic cells with the exception of some adult pluripotent stem cells and male germline cells[2,3]. However, in 85–90% of primary tumours, telomerase is reactivated, so that the ends of chromosomes are maintained during cells proliferation, which results in unlimited proliferation and immortalisation of tumour cells[4]. Therefore, telomerase is regarded as an effective drug target[5]. Regulating the stability of telomerase G-quadruplex as anticancer agents have been widely reported[6–13].

A lot of studies confirmed that dyskerin, fragment protein of telomerase was essential for telomerase activity, which allowed the correct assembly and stabilisation of mature human telomerase RNA (hTR)[14]. Highly expressed dyskerin was closely related to the occurrence and development of various tumours[15–17]. Considering that most cancers rely on the holoenzyme telomerase to promote tumorigenesis and development, and that dyskerin was closely related to the maintenance of telomeres. So, this protein was a potential target for development of anticancer therapies[18].

Several studies had shown that some flavonoid derivatives had strong telomerase inhibitory activity and extensive antitumor activity[19–24]. In our previous work[22], myricetin derivatives exhibited moderate telomerase inhibitory activity (Figure 1(A)), and the preliminary structure–activity relationships (SARs) showed that the introduction of amide segment could significantly change the telomerase inhibitory activity and cytotoxicity. This indicated that the linker should be involved in the improvement of inhibitory activity (Figure 1(B)). In addition, the amount of methoxy groups on the benzene ring has an essential effect on antitumor activity, such as natural **A4**. Therefore, on basis of the above, the optimisation design of the structure was carried out in this study (Figure 1(C)).

As is known to us, 1,3,4-oxadiazole as a privileged scaffold was used extensively in drugs discovery[25–28]. It was often used as bioisosteres for compounds containing carbonyl such as esters and amides, participating in hydrogen bonding interactions with the receptors[29–33]. Furthermore, different substituted 1,3,4-oxadiazole derivatives with potent antitumor activity have been confirmed (Figure 1(D)). Therefore, 2-phenyl-4H-chromone used as a basic scaffold, following by adjusting the number and substitution positions of OCH_3 and H on the phenyl ring, retaining the amide fragment as a linker, then introducing 1,3,4-oxadiazole heterocycle and continuing unsaturated substituent. At last, a series of new 2-phenyl-4H-chromone derivatives were designed and synthesised in this study (Figure 1(E)). Their telomerase inhibitory activity was evaluated, and the SAR was widely discussed. In addition, some compounds were selected to screen for their anticancer activity and explore the possible mechanism.

2. Experimental section

2.1. Chemistry

All reagents and solvents were purchased from standard commercial suppliers and used without further purification. The reactions were monitored by thin-layer chromatography (TLC) on pre-coated

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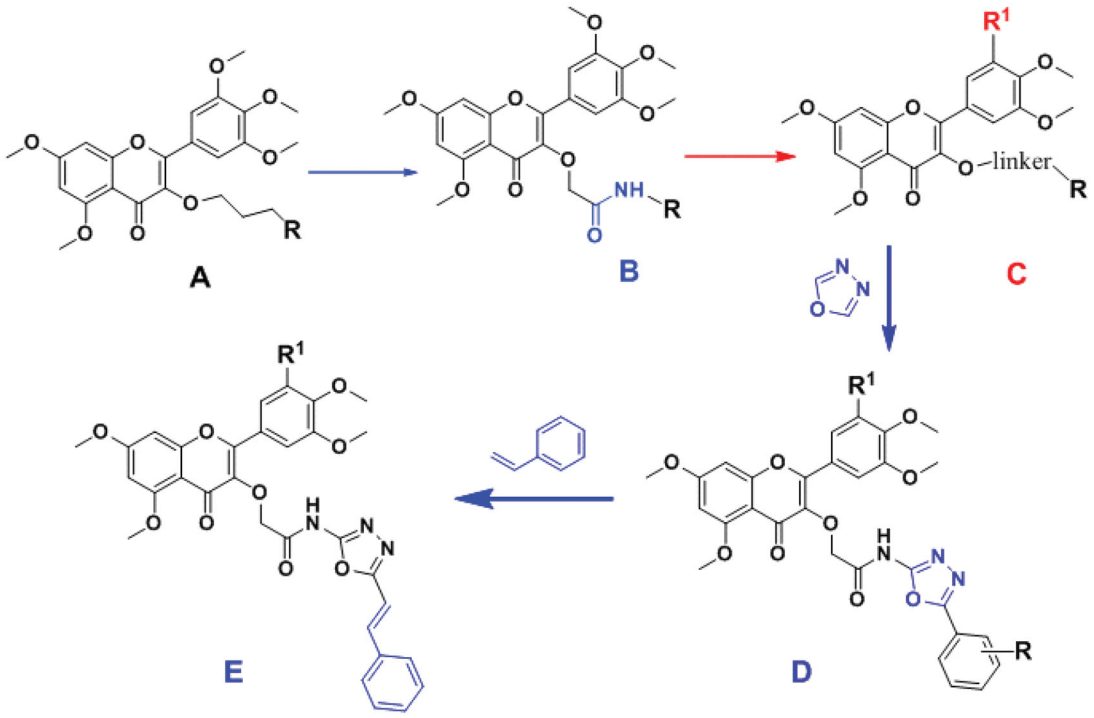


Figure 1. Design of the title compounds.

silica GF254 plates and visualised under UV light at 254 and 365 nm. Melting points (uncorrected) were determined on a XT4MP apparatus (Taike Corp., Beijing, China). ^{1}H and ^{13}C NMR spectral data were recorded on a Bruker 400 MHz or an Agilent 600 MHz spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as the internal standard at room temperature. High-resolution mass spectrometry (HRMS) was recorded on an Agilent Technologies LC-TOF instrument (Supporting Material). X-ray crystallographic data were collected on a Bruker SMART APEX-II CCD diffractometer.

2.2. General procedure for synthesis of title compounds A1-A33 and B1-B33

To a solution of the intermediate **1** (0.5 mmol, in acetone (20 ml), the intermediate **4** (0.48 mmol), K_2CO_3 (0.96 mmol) and KI (cat) were added. The reaction mixture was stirred at the reflux temperature for 12 h, monitored by TLC. After the reaction was completed, the reaction mixture was cooled to room temperature, diluted with water, extracted with CH_2Cl_2 (50 ml × 3), and washed with saturated sodium chloride. The combined organic layers were dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (DCM: MeOH = 25:1, v/v), and then recrystallized by ethanol to give title compounds **A1**–**A33**. The title compounds **B1**–**B33** could be obtained according to the same procedure.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide **(A1)**. White solid, 46.23% yield, m.p.: 222–224 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.62 (s, 1H), 8.12–8.06 (m, 2H), 7.54–7.45 (m, 3H), 7.25 (s, 2H), 6.57 (d, J = 2.2 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 4.40 (s, 2H), 4.00 (s, 3H), 3.95 (s, 3H), 3.94 (s, 6H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.1, 161.5, 161.1, 159.1, 156.9, 154.4, 153.6 (2 C), 141.1, 141.1, 131.3, 128.9 (2 C), 126.7(2 C), 124.4, 123.9, 108.5, 105.9 (2 C), 96.5, 92.8, 73.4, 61.1, 56.6, 56.5(2 C), 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{28}N_3O_{10}$: 590.1769; found: 590.1767.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A2)**. White solid, 47.60% yield, m.p.: 221–223 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.56 (s, 1H), 8.11–8.07 (m, 2H), 7.25 (s, 2H), 7.18 (t, J = 8.6 Hz, 2H), 6.57 (d, J = 2.1 Hz, 1H), 6.43 (d, J = 2.1 Hz, 1H), 4.41 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.95 (s, 6H), 3.94 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 165.1, 164.6 (d, J = 252.6 Hz), 161.1, 160.7, 159.1, 156.9, 154.4, 153.6 (2 C), 141.1 (2 C), 128.9 (d, J = 8.8 Hz) (2 C), 124.4, 120.2 (d, J = 3.2 Hz), 116.2 (d, J = 22.4 Hz) (2 C), 108.5, 105.9 (2 C), 96.5, 92.8, 73.4, 61.06, 56.6, 56.5 (2 C), 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}FN_3O_{10}$: 608.1675; found: 608.1674.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(3-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A3)**. White solid, 35.83% yield, m.p.: 217–219 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.77 (s, 1H), 7.91–7.87 (m, 1H), 7.79 (ddd, J = 9.2, 2.5, 1.5 Hz, 1H), 7.47 (td, J = 8.1, 5.6 Hz, 1H), 7.25 (s, 2H), 7.21 (tdd, J = 8.4, 2.6, 0.9 Hz, 1H), 6.57 (d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 4.40 (s, 2H), 4.01 (s, 3H), 3.96 (s, 3H), 3.95 (s, 6H), 3.94 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.1, 162.8 (d, J = 247.6 Hz), 161.2, 160.5, 159.1, 157.1, 154.4, 153.6 (2 C), 141.3, 141.1, 130.7 (d, J = 7.2 Hz), 125.8 (d, J = 8.2 Hz), 124.4, 122.4, 118.3 (d, J = 20.9 Hz), 113.7 (d, J = 24.3 Hz), 108.5, 106.2 (2 C), 96.5, 92.8, 73.4, 60.99, 56.5 (3 C), 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}FN_3O_{10}$: 608.1675; found: 608.1672.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(2-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A4)**. White solid, 44.80% yield, m.p.: 213–215 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.73 (s, 1H), 8.04 (t, J = 7.0 Hz, 1H), 7.49 (dd, J = 12.0, 6.8 Hz, 1H), 7.27–7.20 (m, 4H), 6.54 (d, J = 1.4 Hz, 1H), 6.40 (s, 1H), 4.39 (s, 2H), 3.98 (s, 3H), 3.96–3.90 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.7, 165.1, 161.1, 159.9 (d, J = 258.4 Hz), 159.0, 158.1 (d, J = 4.9 Hz), 157.2, 154.4, 153.5 (2 C), 141.1, 141.0, 133.1 (d, J = 8.2 Hz), 129.6, 124.5 (d, J = 3.3 Hz), 124.4, 116.8 (d,

$J = 20.8$ Hz),112.4 (d, $J = 11.9$ Hz), 108.4, 105.97 (2 C), 96.47, 92.72, 73.36, 61.01, 56.50 (3 C), 55.94. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}FN_3O_{10}$: 608.1675; found: 608.1671.

N-(5–(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)acetamide **(A5)**. White solid, 49.06% yield, m.p.: 227–229 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.69 (s, 1H), 8.02 (d, $J = 8.5$ Hz, 2H), 7.47 (d, $J = 8.5$ Hz, 2H), 7.25 (s, 2H), 6.56 (d, $J = 1.9$ Hz, 1H), 6.42 (d, $J = 1.7$ Hz, 1H), 4.40 (s, 2H), 4.00 (s, 3H), 3.99–3.90 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.6, 165.1, 161.1, 160.7, 159.1, 157.0, 154.5, 153.6 (2 C), 141.2, 141.1, 137.6, 129.3 (2 C), 127.9 (2 C), 124.4, 122.3, 108.5, 106.0 (2 C), 96.5, 92.8, 73.4, 61.1, 56.6, 56.5(2 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}ClN_3O_{10}$: 624.1379; found: 624.1376.

N-(5–(3-chlorophenyl)-1,3,4-oxadiazol-2-yl)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)acetamide **(A6)**. White solid, 52.33% yield, m.p.: 206–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.81 (s, 1H), 8.07 (t, $J = 1.6$ Hz, 1H), 7.99 (dt, $J = 7.5$, 1.2 Hz, 1H), 7.50–7.46 (m, 1H), 7.43 (t, $J = 7.8$ Hz, 1H), 7.25 (s, 2H), 6.57 (d, $J = 2.0$ Hz, 1H), 6.42 (d, $J = 2.0$ Hz, 1H), 4.40 (s, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 3.94 (d, $J = 2.7$ Hz, 6H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.6, 165.1, 161.1, 160.2, 159.0, 157.2, 154.4, 153.6 (2 C), 141.2, 141.1, 135.0, 131.3, 130.2, 126.6, 125.5, 124.8, 124.4, 108.4, 106.0 (2 C), 96.5, 92.8, 73.4, 61.0, 56.5 (3 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}ClN_3O_{10}$: 624.1379; found: 624.1375.

N-(5–(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)acetamide **(A7)**. White solid, 43.61% yield, m.p.: 201–203 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.78 (s, 1H), 7.99 (d, $J = 7.7$ Hz, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.47–7.36 (m, 2H), 7.25 (s, 2H), 6.56 (d, $J = 1.9$ Hz, 1H), 6.41 (d, $J = 1.7$ Hz, 1H), 4.40 (s, 2H), 3.99 (s, 3H), 3.97–3.91 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.6, 165.1, 161.2, 159.7, 159.0, 157.3, 154.4, 153.6 (2 C), 141.1, 141.1, 133.2, 132.0, 131.2, 131.0, 126.9, 124.4, 123.2, 108.5, 106.0 (2 C), 96.5, 92.7, 73.4, 61.1, 56.5 (3 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}ClN_3O_{10}$: 624.1379; found: 624.1377.

N-(5–(4-bromophenyl)-1,3,4-oxadiazol-2-yl)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)acetamide **(A8)**. White solid, 50.89% yield, m.p.: 234–236 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.67 (s, 1H), 7.96 (d, $J = 8.4$ Hz, 2H), 7.63 (d, $J = 8.4$ Hz, 2H), 7.25 (s, 2H), 6.57 (s, 1H), 6.43 (s, 1H), 4.40 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.95 (s, 6H), 3.94 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.6, 165.1, 161.1, 160.8, 159.1, 157.0, 154.5, 153.6 (2 C), 141.2, 141.1, 132.2 (2 C), 128.1 (2 C), 125.9, 124.4, 122.8, 108.5, 106.0 (2 C), 96.5, 92.8, 73.4, 61.1, 56.6, 56.5 (2 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}BrN_3O_{10}$: 668.0874; found: 668.0873.

N-(5–(3-bromophenyl)-1,3,4-oxadiazol-2-yl)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)acetamide **(A9)**. White solid, 45.80% yield, m.p.: 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.84 (s, 1H), 8.23 (s, 1H), 8.03 (d, $J = 7.8$ Hz, 1H), 7.66–7.61 (m, 1H), 7.36 (t, $J = 7.9$ Hz, 1H), 7.25 (s, 2H), 6.57 (d, $J = 2.0$ Hz, 1H), 6.42 (d, $J = 2.1$ Hz, 1H), 4.40 (s, 2H), 4.01 (s, 3H), 3.96 (s, 3H), 3.94 (s, 6H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.6, 165.1, 161.2, 160.1, 159.1, 157.2, 154.5, 153.6 (2 C), 141.2, 141.1, 134.3, 130.4, 129.5, 125.7, 125.2, 124.4, 122.9, 108.5, 106.0 (2 C), 96.5, 92.8, 73.4, 61.0, 56.6, 56.5 (2 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}BrN_3O_{10}$: 668.0874; found: 668.0871.

N-(5–(2-bromophenyl)-1,3,4-oxadiazol-2-yl)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)acetamide **(A10)**. White solid, 53.94% yield, m.p.: 199–201 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.77 (s, 1H), 7.93 (d, $J = 7.7$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.43 (t, $J = 7.6$ Hz, 1H), 7.35 (dd, $J = 10.9$, 4.5 Hz, 1H), 7.24 (s, 2H), 6.55 (d, $J = 1.9$ Hz, 1H), 6.41 (d, $J = 1.8$ Hz, 1H), 4.40 (s, 2H), 3.98 (s, 3H), 3.96–3.90 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.1, 161.2, 160.2, 159.0, 157.3, 154.4, 153.6 (2 C), 141.2, 141.1, 134.3, 132.1, 131.6, 127.4, 125.4, 124.4, 121.7, 108.5, 106.1 (2 C), 96.5, 92.8, 73.4, 61.0, 56.6 (2 C), 56.5, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}BrN_3O_{10}$: 668.0874; found: 668.0873.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5-p-tolyl-1,3,4-oxadiazol-2-yl)acetamide **(A11)**. White solid, 46.21% yield, m.p.: 225–227 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.45 (s, 1H), 7.98 (d, $J = 8.1$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.25 (s, 2H), 6.57 (d, $J = 2.0$ Hz, 1H), 6.43 (d, $J = 1.9$ Hz, 1H), 4.41 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.95 (s, 6H), 3.94 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.0, 161.7, 161.1, 159.1, 156.6, 154.4, 153.6 (2 C), 141.8, 141.1 (2 C), 129.6 (2 C), 126.7 (2 C), 124.4, 121.1, 108.5, 105.9 (2 C), 96.5, 92.7, 73.4, 61.1, 56.6, 56.5 (2 C), 55.9, 21.6. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{30}N_3O_{10}$: 604.1926; found: 604.1922.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5-m-tolyl-1,3,4-oxadiazol-2-yl)acetamide **(A12)**. White solid, 42.83% yield, m.p.: 197–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.60 (s, 1H), 7.92 (s, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 7.37 (t, $J = 7.6$ Hz, 1H), 7.31 (d, $J = 7.7$ Hz, 1H), 7.25 (s, 2H), 6.57 (d, $J = 2.2$ Hz, 1H), 6.42 (d, $J = 2.2$ Hz, 1H), 4.40 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.95 (s, 6H), 3.93 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.1, 161.7, 161.2, 159.1, 156.8, 154.4, 153.6 (2 C), 141.1, 141.1, 138.7, 132.1, 128.8, 127.2, 124.4, 123.9, 123.7, 108.5, 106.0 (2 C), 96.5, 92.8, 73.4, 61.1, 56.5, 56.5 (2 C), 55.9, 21.2. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{30}N_3O_{10}$: 604.1926; found: 604.1924.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5-o-tolyl-1,3,4-oxadiazol-2-yl)acetamide **(A13)**. White solid, 45.08% yield, m.p.: 205–207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.64 (s, 1H), 8.00–7.95 (m, 1H), 7.42–7.36 (m, 1H), 7.34 − 7.27 (m, 2H), 7.25 (s, 2H), 6.56 (d, $J = 2.2$ Hz, 1H), 6.41 (d, $J = 2.2$ Hz, 1H), 4.40 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 3.94 (s, 6H), 3.93 (s, 3H), 2.72 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.0, 161.8, 161.2, 159.0, 156.7, 154.4, 153.6 (2 C), 141.1, 141.1, 138.3, 131.5, 130.8, 128.9, 125.9, 124.4, 122.9, 108.5, 106.0 (2 C), 96.5, 92.7, 73.4, 61.0, 56.5, 56.5 (2 C), 55.9, 21.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{30}N_3O_{10}$: 604.1926; found: 604.1923.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A14)**. Light yellow solid, 42.89% yield, m.p.: 233–235 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.01 (s, 1H), 8.89 (s, 1H), 8.44 (d, $J = 7.8$ Hz, 1H), 8.36 (dd, $J = 8.2$, 1.1 Hz, 1H), 7.70 (t, $J = 8.0$ Hz, 1H), 7.25 (s, 2H), 6.57 (d, $J = 2.0$ Hz, 1H), 6.43 (d, $J = 1.8$ Hz, 1H), 4.41 (s, 2H), 4.02 (s, 3H), 3.97–3.92 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 166.7, 165.2, 161.2, 159.4, 159.1, 157.6, 154.6, 153.6 (2 C), 148.6, 141.2, 141.1, 132.2, 130.2, 125.7, 125.5, 124.3, 121.5, 108.4, 105.9 (2 C), 96.5, 92.8, 73.5, 61.0, 56.5(2 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}N_4O_{12}$: 635.1620; found: 635.1620.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(2-nitrophenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A15)**. Light yellow solid, 45.03% yield, m.p.: 204–206 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.99 (s, 1H), 8.08 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.98 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.77 (td, $J = 7.6$, 1.3 Hz, 1H), 7.73 (td, $J = 7.8$, 1.5 Hz, 1H), 7.24 (s, 2H), 6.56 (d, $J = 2.2$ Hz, 1H), 6.41 (d, $J = 2.2$ Hz, 1H), 4.38 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 3.95 (s, 6H), 3.93 (s, 3H). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}N_4O_{12}$: 635.1620; found: 635.1619.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A16)**. White solid, 51.73% yield, m.p.: 231–233 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.78 (s, 1H), 8.22 (d, $J = 8.2$ Hz, 2H), 7.75 (d,

$J = 8.3$ Hz, 2H), 7.25 (s, 2H), 6.57 (s, 1H), 6.43 (d, $J = 1.7$ Hz, 1H), 4.41 (s, 2H), 4.01 (s, 3H), 3.96 (s, 3H), 3.95 (s, 6H), 3.94 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.6, 165.1, 161.1, 160.3, 159.1, 157.4, 154.5, 153.6(2 C), 141.3, 141.1, 132.94 (m),127.1, 126.9 (2 C), 125.9 (d, $J = 3.6$ Hz) (2 C), 124.4, 123.6, 108.5, 106.1 (2 C), 96.5, 92.8, 73.4, 61.0, 56.5 (3 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}F_3N_3O_{10}$: 658.1643; found: 658.1641.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A17)**. White solid, 54.83% yield, m.p.: 220–222 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.87 (s, 1H), 8.33 (s, 1H), 8.28 (d, $J = 7.7$ Hz, 1H), 7.76 (d, $J = 7.6$ Hz, 1H), 7.63 (t, $J = 7.7$ Hz, 1H), 7.25 (s, 2H), 6.56 (d, $J = 1.6$ Hz, 1H), 6.42 (d, $J = 1.6$ Hz, 1H), 4.40 (s, 2H), 3.99 (s, 3H), 3.98–3.89 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 166.7, 165.1, 161.1, 160.2, 159.1, 157.3, 154.5, 153.6 (2 C), 141.2, 141.1, 131.6, 129.8, 129.6, 127.8, 124.7, 124.3, 123.6, 123.5, 108.4, 106.0 (2 C), 96.5, 92.8, 73.4, 61.0, 56.5 (3 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}F_3N_3O_{10}$: 658.1643; found: 658.1642.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(2-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A18)**. White solid, 49.66% yield, m.p.: 191–193 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.90 (s, 1H), 8.04 (d, $J = 7.2$ Hz, 1H), 7.85 (d, $J = 7.3$ Hz, 1H), 7.72–7.64 (m, 2H), 7.24 (s, 2H), 6.55 (d, $J = 1.7$ Hz, 1H), 6.41 (d, $J = 1.4$ Hz, 1H), 4.40 (s, 2H), 3.97 (s, 3H), 3.96–3.91 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.5, 165.1, 161.3, 159.4, 159.0, 157.9, 154.4, 153.6 (2 C), 141.2, 141.1, 131.9, 131.9, 131.2, 129.0, 126.8, 124.4, 123.2, 122.5, 108.5, 106.1 (2 C), 96.5, 92.7, 73.4, 60.9, 56.5 (2 C), 56.4, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}F_3N_3O_{10}$: 658.1643; found: 658.1641.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(4-(trifluoromethoxy)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A19)**. White solid, 51.51% yield, m.p.: 230–232 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.62 (s, 1H), 8.13 (d, $J = 8.6$ Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 2H), 7.25 (s, 2H), 6.56 (d, $J = 1.4$ Hz, 1H), 6.42 (d, $J = 1.2$ Hz, 1H), 4.41 (s, 2H), 3.99 (s, 3H), 3.96–3.92 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.1, 161.2, 160.4, 159.1, 157.1, 154.4, 153.6 (2 C), 151.3 (d, $J = 1.5$ Hz), 141.3, 141.1, 128.4 (2 C), 124.4, 122.5, 121.1 (2 C), 120.3, 108.5, 106.1 (2 C), 96.5, 92.8, 73.3, 61.0, 56.6 (2 C), 56.5, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}F_3N_3O_{11}$: 674.1592; found: 674.1590.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(3-(trifluoromethoxy)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A20)**. White solid, 46.65% yield, m.p.: 221–223 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.73 (s, 1H), 8.04 (d, $J = 7.7$ Hz, 1H), 7.94 (s, 1H), 7.53 (t, $J = 8.0$ Hz, 1H), 7.37 (d, $J = 7.4$ Hz, 1H), 7.25 (s, 2H), 6.57 (d, $J = 1.9$ Hz, 1H), 6.43 (d, $J = 1.7$ Hz, 1H), 4.41 (s, 2H), 4.00 (s, 3H), 3.98–3.92 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.6, 165.1, 161.2, 160.2, 159.1, 157.2, 154.4, 153.6 (2 C), 149.6, 141.3, 141.1, 130.5, 125.8, 124.9, 124.4, 123.6, 120.4, 119.2, 108.5, 106.1 (2 C), 96.5, 92.8, 73.4, 61.0, 56.6 (2 C), 56.5, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}F_3N_3O_{11}$: 674.1592; found: 674.1593.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(2-(trifluoromethoxy)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A21)**. White solid, 35.65% yield, m.p.: 202–204 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.75 (s, 1H), 8.16 (dd, $J = 7.7$, 1.1 Hz, 1H), 7.59–7.54 (m, 1H), 7.44 (t, $J = 7.7$ Hz, 2H), 7.25 (s, 2H), 6.55 (d, $J = 2.0$ Hz, 1H), 6.41 (d, $J = 1.9$ Hz, 1H), 4.41 (s, 2H), 3.98 (s, 3H), 3.97–3.90 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.5, 165.0, 161.3, 159.0, 158.4, 157.5, 154.3, 153.6 (2 C), 146.4 (d, $J = 1.7$ Hz),141.2, 141.1, 132.5, 130.5, 127.2, 124.4, 122.1, 120.5, 118.2, 108.6, 106.1 (2 C), 96.5, 92.7, 73.4, 61.0, 56.5 (2 C), 56.4, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}F_3N_3O_{11}$: 674.1592; found: 674.1592.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A22)**. White solid, 38.43% yield, m.p.: 239–241 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.41 (s, 1H), 8.01 (d, $J = 8.5$ Hz, 2H), 7.25 (s, 2H), 6.98 (d, $J = 8.6$ Hz, 2H), 6.56 (d, $J = 1.5$ Hz, 1H), 6.42 (d, $J = 1.3$ Hz, 1H), 4.40 (s, 2H), 4.00 (s, 3H), 3.98–3.92 (m, 12H), 3.87 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.0, 162.1, 161.6, 161.1, 159.1, 156.4, 154.32, 153.6 (2 C), 141.1, 141.1, 128.5 (2 C), 124.5, 116.4, 114.3 (2 C), 108.5, 105.9 (2 C), 96.5, 92.8, 73.3, 61.1, 56.6, 56.5(2 C), 55.9, 55.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{30}N_3O_{11}$: 620.1875; found: 620.1871.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A23)**. White solid, 43.92% yield, m.p.: 208–210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.63 (s, 1H), 7.68–7.64 (m, 1H), 7.63–7.61 (m, 1H), 7.39 (t, $J = 8.0$ Hz, 1H), 7.25 (s, 2H), 7.07–7.03 (m, 1H), 6.57 (d, $J = 2.2$ Hz, 1H), 6.42 (d, $J = 2.2$ Hz, 1H), 4.40 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.95 (s, 6H), 3.93 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.0, 161.5, 161.1, 159.9, 159.1, 156.9, 154.4, 153.6 (2 C), 141.1, 141.1, 129.9, 124.9, 124.4, 119.2, 118.1, 111.2, 108.5, 105.9 (2 C), 96.5, 92.8, 73.4, 61.1, 55.5, 56.6, 56.5 (2 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{30}N_3O_{11}$: 620.1875; found: 620.1873.

N-(5–(3-chloro-4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)acetamide **(A24)**. White solid, 31.79% yield, m.p.: 228–230 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.79 (s, 1H), 8.16 (d, $J = 6.7$ Hz, 1H), 8.03–7.98 (m, 1H), 7.28 (d, $J = 9.2$ Hz, 1H), 7.26 (s, 2H), 6.57 (s, 1H), 6.44 (s, 1H), 4.41 (s, 2H), 4.02 (s, 3H), 3.98–3.93 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.6, 165.1, 161.2, 160.2, 159.1, 159.1, 157.2, 154.5, 153.6 (2 C), 141.3, 141.1, 129.1, 126.8, 124.34, 122.2, 121.2, 117.3, 108.5, 106.1 (2 C), 96.5, 92.8, 73.4, 61.0, 56.6 (3 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{26}ClFN_3O_{10}$: 642.1285; found: 642.1281.

N-(5–(3,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)acetamide **(A25)**. White solid, 36.16% yield, m.p.: 222–224 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.87 (s, 1H), 8.18 (d, $J = 1.8$ Hz, 1H), 7.94 (dd, $J = 8.4$, 1.9 Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.25 (s, 2H), 6.57 (d, $J = 2.0$ Hz, 1H), 6.43 (d, $J = 1.9$ Hz, 1H), 4.40 (s, 2H), 4.02 (s, 3H), 3.98–3.92 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 166.6, 165.1, 161.1, 159.6, 159.1, 157.3, 154.5, 153.6 (2 C), 141.2, 141.1, 135.8, 133.5, 131.1, 128.3, 125.7, 124.3, 123.7, 108.4, 106.0 (2 C), 96.6, 92.8, 73.4, 61.0, 56.6, 56.5 (2 C), 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{26}Cl_2N_3O_{10}$: 658.0990; found: 658.0986.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(3,5-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A26)**. White solid, 47.13% yield, m.p.: 198–200 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.47 (s, 1H), 7.25 (s, 2H), 7.23 (d, $J = 2.2$ Hz, 2H), 6.59 (t, $J = 2.2$ Hz, 1H), 6.56 (d, $J = 2.1$ Hz, 1H), 6.42 (d, $J = 2.1$ Hz, 1H), 4.41 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.95 (s, 6H), 3.94 (s, 3H), 3.86 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.0, 161.5, 161.1, 161.0 (2 C), 159.1, 156.8, 154.4, 153.6 (2 C), 141.1, 141.0, 125.4, 124.4, 108.5, 105.9 (2 C), 104.5(2 C), 104.3, 96.5, 92.8, 73.3, 61.1, 56.6, 56.5 (2 C), 55.9, 55.7 (2 C). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{32}N_3O_{12}$: 650.1980; found: 650.1976.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5–(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)acetamide **(A27)**. White solid, 41.89% yield, m.p.: 220–222 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.36 (s, 1H), 7.64 (d, $J = 8.3$ Hz, 1H), 7.60 (s, 1H), 7.25 (s, 2H), 6.94 (d, $J = 8.4$ Hz, 1H), 6.56 (d, $J = 1.5$ Hz, 1H), 6.42 (d, $J = 1.4$ Hz, 1H), 4.41 (s, 2H), 3.99 (s, 3H), 3.98–3.91 (m, 18H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.5, 166.6, 165.0, 161.7, 161.2,

159.0, 156.5, 154.3, 153.6 (2 C), 151.8, 149.3, 141.2, 141.0, 124.4, 120.3, 116.6, 111.1, 109.5, 108.6, 106.1 (2 C), 96.5, 92.8, 73.3, 61.0, 56.6 (2 C), 56.5, 56.2, 55.9, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{32}N_3O_{12}$: 650.1980; found: 650.1978.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5-(naphthalen-1-yl)-1,3,4-oxadiazol-2-yl)acetamide **(A28)**. White solid, 53.18% yield, m.p.: 238–240 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.59 (s, 1H), 9.27 (d, $J = 8.6$ Hz, 1H), 8.24 (d, $J = 7.1$ Hz, 1H), 8.01 (d, $J = 8.1$ Hz, 1H), 7.91 (d, $J = 8.1$ Hz, 1H), 7.68 (t, $J = 7.6$ Hz, 1H), 7.57 (dd, $J = 17.0$, 8.2 Hz, 2H), 7.27 (s, 2H), 6.56 (s, 1H), 6.42 (s, 1H), 4.45 (s, 2H), 4.00 (s, 3H), 3.98–3.92 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.5, 166.6, 165.0, 161.6, 161.2, 159.1, 156.7, 154.3, 153.6 (2 C), 141.3, 141.1, 133.8, 132.1, 130.0, 128.5, 128.3, 127.9, 126.5, 126.4, 124.8, 124.5, 120.4, 108.6, 106.2 (2 C), 96.5, 92.8, 73.4, 61.0, 56.6 (2 C), 56.5, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{30}N_3O_{10}$: 640.1926; found: 640.1924.

N-(5–(2,3-dihydrobenzo[b][1, 4]dioxin-6-yl)-1,3,4-oxadiazol-2-yl)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)acetamide **(A29)**. White solid, 54.62% yield, m.p.: 231–233 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (s, 1H), 7.60 (d, $J = 2.0$ Hz, 1H), 7.57 (dd, $J = 8.4$, 2.1 Hz, 1H), 7.24 (s, 2H), 6.93 (d, $J = 8.4$ Hz, 1H), 6.56 (d, $J = 2.2$ Hz, 1H), 6.41 (d, $J = 2.2$ Hz, 1H), 4.39 (s, 2H), 4.30 (q, $J = 5.1$ Hz, 4H), 4.00 (s, 3H), 3.95 (s, 3H), 3.94 (s, 6H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.0, 161.3, 161.1, 159.1, 156.5, 154.3, 153.5 (2 C), 146.4, 143.8, 141.1, 141.0, 124.5, 120.4, 117.8, 117.1, 115.9, 108.5, 105.9 (2 C), 96.5, 92.7, 73.4, 64.6, 64.2, 61.1, 56.6, 56.5 (2 C), 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{30}N_3O_{12}$: 648.1824; found: 648.1821.

N-(5–(3-(benzyloxy)phenyl)-1,3,4-oxadiazol-2-yl)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)acetamide **(A30)**. White solid, 44.01% yield, m.p.: 188–190 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.54 (s, 1H), 7.73 (s, 1H), 7.68 (d, $J = 7.6$ Hz, 1H), 7.46 (d, $J = 7.3$ Hz, 2H), 7.39 (t, $J = 7.7$ Hz, 3H), 7.33 (t, $J = 7.2$ Hz, 1H), 7.26 (s, 2H), 7.15–7.10 (m, 1H), 6.56 (d, $J = 1.7$ Hz, 1H), 6.42 (d, $J = 1.6$ Hz, 1H), 5.14 (s, 2H), 4.41 (s, 2H), 3.99 (s, 3H), 3.98–3.91 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.1, 161.4, 161.1, 159.1, 156.9, 154.4, 153.6, 141.1, 141.0, 136.5, 130.1, 128.6, 128.1, 127.6, 125.0, 124.4, 119.44, 118.6, 112.4, 108.5, 106.0, 96.5, 92.7, 73.4, 70.3, 61.0, 56.5, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{34}N_3O_{11}$: 696.2188; found: 696.2183.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)acetamide **(A31)**. White solid, 49.30% yield, m.p.: 240–242 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.64 (s, 1H), 7.61 (d, $J = 0.9$ Hz, 1H), 7.24 (s, 2H), 7.16 (d, $J = 3.2$ Hz, 1H), 6.57 (dd, $J = 3.4$, 1.7 Hz, 1H), 6.56 (d, $J = 2.1$ Hz, 1H), 6.42 (d, $J = 1.9$ Hz, 1H), 4.39 (s, 2H), 4.00 (s, 3H), 3.97–3.92 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.0, 161.2, 159.1, 156.3, 154.4, 154.4, 153.6 (2 C), 145.3, 141.2, 141.1, 139.3, 124.4, 113.5, 111.9, 108.5, 106.1 (2 C), 96.5, 92.8, 73.3, 61.0, 56.5 (3 C), 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_{11}$: 580.1562; found: 580.1562.

2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5-(thiophen-2-yl)-1,3,4-oxadiazol-2-yl)acetamide **(A32)**. White solid, 45.68% yield, m.p.: 224–226 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.60 (s, 1H), 7.78 (dd, $J = 3.7$, 1.1 Hz, 1H), 7.52 (dd, $J = 5.0$, 1.0 Hz, 1H), 7.25 (s, 2H), 7.15 (dd, $J = 5.0$, 3.8 Hz, 1H), 6.57 (d, $J = 2.2$ Hz, 1H), 6.42 (d, $J = 2.2$ Hz, 1H), 4.39 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.94 (s, 6H), 3.94 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 165.1, 161.1, 159.0, 157.9, 156.3, 154.4, 153.6 (2 C), 141.2, 141.0, 129.6, 129.5, 127.9, 125.2, 124.4, 108.5, 106.1 (2 C), 96.5, 92.8, 73.3, 61.0, 56.5 (3 C), 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_{10}S$: 596.1333; found: 596.1330.

(E)-2–(5,7-dimethoxy-4-oxo-2–(3,4,5-trimethoxyphenyl)-4H-chromen-3-yloxy)-N-(5-styryl-1,3,4-oxadiazol-2-yl)acetamide **(A33)**. White solid, 45.31% yield, m.p.: 223–225 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.59 (s, 1H), 7.57 (d, $J = 16.7$ Hz, 1H), 7.54 (d, $J = 7.4$ Hz, 2H), 7.43–7.34 (m, 3H), 7.25 (s, 2H), 7.02 (d, $J = 16.4$ Hz, 1H), 6.57 (d, $J = 2.0$ Hz, 1H), 6.43 (d, $J = 1.9$ Hz, 1H), 4.40 (s, 2H), 4.01 (s, 3H), 3.98 − 3.92 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.5, 165.1, 161.2, 161.1, 159.1, 156.4, 154.4, 153.6 (2 C), 141.1, 141.2, 138.2, 134.8, 129.7, 128.9 (2 C), 127.4 (2 C), 124.4, 109.9, 108.5, 105.9 (2 C), 96.5, 92.8, 73.4, 61.0, 56.6, 56.6 (2 C), 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{30}N_3O_{10}$: 616.1926; found: 616.1924.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide **(B1)**. White solid, 46.92% yield, m.p.: 237–239 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.57 (s, 1H), 8.09 (d, $J = 6.9$ Hz, 2H), 7.67 (d, $J = 8.5$ Hz, 1H), 7.55 (s, 1H), 7.53–7.46 (m, 3H), 7.01 (d, $J = 8.5$ Hz, 1H), 6.56 (s, 1H), 6.41 (s, 1H), 4.40 (s, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.8, 164.9, 161.6, 161.2, 159.1, 156.9, 154.6, 151.9, 149.4, 140.8, 131.3, 128.9 (2 C), 126.8 (2 C), 123.9, 122.3, 121.9, 111.4, 111.1, 108.6, 96.5, 92.8, 73.3, 56.6, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{26}N_3O_9$: 560.1664; found: 560.1665.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B2)**. White solid, 54.11% yield, m.p.: 236–238 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.61 (s, 1H), 8.12–8.06 (m, 2H), 7.67 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.54 (d, $J = 1.9$ Hz, 1H), 7.17 (dd, $J = 12.0$, 5.3 Hz, 2H), 7.02 (d, $J = 8.6$ Hz, 1H), 6.57 (d, $J = 2.2$ Hz, 1H), 6.41 (d, $J = 2.1$ Hz, 1H), 4.40 (s, 2H), 4.01–3.96 (m, 9H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.7, 164.9, 164.6, 161.1, 160.67, 159.0, 156.9, 154.5, 151.9, 149.3, 140.8, 128.9 (2 C), 122.2, 121.8, 120.3, 116.2 (2 C), 111.3, 110.9, 108.5, 96.4, 92.8, 73.2, 56.5, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}FN_3O_9$: 578.1569; found: 578.1569.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(3-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B3)**. White solid, 34.63% yield, m.p.: 229–231 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.77 (s, 1H), 7.89 (d, $J = 6.8$ Hz, 1H), 7.79 (d, $J = 8.2$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.55 (s, 1H), 7.47 (d, $J = 6.2$ Hz, 1H), 7.21 (d, $J = 7.2$ Hz, 1H), 7.02 (d, $J = 7.8$ Hz, 1H), 6.57 (s, 1H), 6.42 (s, 1H), 4.40 (s, 2H), 4.04–3.90 (m, 12H). HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}FN_3O_9$: 578.1569; found: 578.1568.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(2-fluorophenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B4)**. White solid, 38.97% yield, m.p.: 235–237 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.70 (s, 1H), 8.07 (t, $J = 7.0$ Hz, 1H), 7.67 (d, $J = 8.2$ Hz, 1H), 7.54 (s, 1H), 7.50 (q, $J = 11.4$, 6.7 Hz, 1H), 7.28 (d, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 9.3$ Hz, 1H), 7.01 (d, $J = 8.5$ Hz, 1H), 6.56 (s, 1H), 6.41 (d, $J = 0.8$ Hz, 1H), 4.40 (s, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.7, 164.9, 161.2, 159.9 (d, $J = 258.7$ Hz), 159.0, 158.2, 157.2, 154.5, 151.9, 149.3, 140.7, 132.9, 129.7, 124.4, 122.2, 121.9, 116.8, 112.6, 111.4, 111.1, 108.6, 96.4, 92.7, 73.2, 56.5, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}FN_3O_9$: 578.1569; found: 578.1567.

N-(5–(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B5)**. White solid, 42.10% yield, m.p.: 213–215 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.75 (s, 1H), 8.01 (d, $J = 8.1$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 1H), 7.54 (s, 1H), 7.46 (d, $J = 8.2$ Hz, 2H), 7.01 (d, $J = 8.5$ Hz, 1H), 6.56 (s, 1H), 6.40 (s, 1H), 4.39 (s, 2H), 4.03–3.95 (m, 9H), 3.92 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 164.9, 161.1, 160.6, 159.0, 157.1, 154.6, 151.9, 149.3, 140.7, 137.5, 129.2 (2 C), 127.9 (2 C), 122.4, 122.2, 121.8, 111.3, 110.9, 108.4, 96.4, 92.7, 73.2, 56.5,

56.2, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}ClN_3O_9$: 594.1274; found: 594.1272.

N-(5–(3-chlorophenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B6)**. White solid, 45.24% yield, m.p.: 220–222 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.81 (s, 1H), 8.08 (s, 1H), 7.99 (d, $J=7.7$ Hz, 1H), 7.68 (dd, $J=8.5$, 1.8 Hz, 1H), 7.54 (d, $J=1.7$ Hz, 1H), 7.48 (d, $J=8.1$ Hz, 1H), 7.43 (t, $J=7.9$ Hz, 1H), 7.02 (d, $J=8.6$ Hz, 1H), 6.57 (d, $J=2.0$ Hz, 1H), 6.41 (d, $J=1.9$ Hz, 1H), 4.40 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 164.9, 161.1, 160.2, 159.0, 157.2, 154.6, 151.9, 149.3, 140.7, 135.0, 131.3, 130.2, 126.6, 125.5, 124.7, 122.2, 121.8, 111.4, 111.1, 108.4, 96.4, 92.8, 73.2, 56.5, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}ClN_3O_9$: 594.1274; found: 594.1271.

N-(5–(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B7)**. White solid, 31.57% yield, m.p.: 221–223 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.73 (s, 1H), 8.00 (dd, $J=7.7$, 1.4 Hz, 1H), 7.67 (dd, $J=8.5$, 1.9 Hz, 1H), 7.56 − 7.52 (m, 2H), 7.44 (td, $J=7.8$, 1.5 Hz, 1H), 7.38 (td, $J=7.6$, 0.8 Hz, 1H), 7.02 (d, $J=8.6$ Hz, 1H), 6.56 (d, $J=2.0$ Hz, 1H), 6.41 (d, $J=2.0$ Hz, 1H), 4.40 (s, 2H), 3.99–3.96 (m, 9H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 164.9, 161.1, 159.6, 159.0, 157.3, 154.5, 151.8, 149.3, 140.8, 133.2, 132.0, 131.2, 131.0, 126.9, 123.3, 122.2, 121.8, 111.3,110.9, 108.5, 96.4, 92.7, 73.3, 56.5, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}ClN_3O_9$: 594.1274; found: 594.1270.

N-(5–(4-bromophenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B8)**. White solid, 44.05% yield, m.p.: 212–214 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.73 (s, 1H), 7.98–7.94 (m, 2H), 7.68 (dd, $J=8.5$, 2.0 Hz, 1H), 7.65–7.61 (m, 2H), 7.54 (d, $J=2.0$ Hz, 1H), 7.02 (d, $J=8.6$ Hz, 1H), 6.57 (d, $J=2.1$ Hz, 1H), 6.42 (d, $J=2.1$ Hz, 1H), 4.39 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 164.9, 161.1, 160.7, 159.0, 157.1, 154.6, 151.9, 149.3, 140.8, 132.2 (2 C), 128.1 (2 C), 125.9, 122.8, 122.2, 121.8, 111.3, 110.9, 108.5, 96.4, 92.8, 73.3, 56.5, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}BrN_3O_9$: 638.0769; found: 638.0764.

N-(5–(3-bromophenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B9)**. White solid, 39.16% yield, m.p.: 204–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.87 (s, 1H), 8.24 (t, $J=1.7$ Hz, 1H), 8.07–8.02 (m, 1H), 7.68 (dd, $J=8.5$, 2.1 Hz, 1H), 7.65–7.62 (m, 1H), 7.55 (d, $J=2.0$ Hz, 1H), 7.37 (t, $J=7.9$ Hz, 1H), 7.02 (d, $J=8.6$ Hz, 1H), 6.58 (d, $J=2.2$ Hz, 1H), 6.42 (d, $J=2.2$ Hz, 1H), 4.40 (s, 2H), 4.01 (s, 3H), 3.99 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 164.9, 161.1, 160.0, 159.0, 157.2, 154.6, 151.9, 149.3, 140.8, 134.2, 130.4, 129.4, 125.7, 125.2, 122.9, 122.2, 121.8, 111.3, 110.9, 108.4, 96.4, 92.7, 73.3, 56.6, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}BrN_3O_9$: 638.0769; found: 638.0765.

N-(5–(2-bromophenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B10)**. White solid, 48.95% yield, m.p.: 226–228 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.80 (s, 1H), 7.94 (d, $J=7.6$ Hz, 1H), 7.73 (d, $J=8.0$ Hz, 1H), 7.67 (d, $J=8.4$ Hz, 1H), 7.54 (s, 1H), 7.43 (t, $J=7.5$ Hz, 1H), 7.35 (t, $J=7.7$ Hz, 1H), 7.01 (d, $J=8.5$ Hz, 1H), 6.55 (s, 1H), 6.40 (s, 1H), 4.40 (s, 2H), 4.00–3.95 (m, 9H), 3.92 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 164.9, 161.2, 160.2, 159.0, 157.4, 154.5, 151.9, 149.4, 140.7, 134.3, 132.1, 131.6, 127.3, 125.5, 122.2, 121.9, 121.7, 111.4, 111.1, 108.5, 96.4, 92.8, 73.24, 56.5, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}BrN_3O_9$: 638.0769; found: 638.0766.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5-p-tolyl-1,3,4-oxadiazol-2-yl)acetamide **(B11)**. White solid, 41.50% yield, m.p.: 239–241 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.53 (s, 1H), 7.97 (d, $J=8.1$ Hz, 2H), 7.67 (dd, $J=8.5$, 1.9 Hz, 1H), 7.54 (d, $J=1.6$ Hz, 1H), 7.28 (d, $J=7.9$ Hz, 2H), 7.01 (d, $J=8.6$ Hz, 1H), 6.56 (d, $J=2.0$ Hz, 1H), 6.40 (d, $J=1.9$ Hz, 1H), 4.39 (s, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 164.9, 161.6, 161.1, 159.0, 156.7, 154.5, 151.8, 149.3, 141.8, 140.7, 129.5 (2 C), 126.7 (2 C), 122.2, 121.8, 121.1, 111.3, 110.9, 108.5, 96.4, 92.7, 73.2, 56.5, 56.2, 56.1, 55.9, 21.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{28}N_3O_9$: 574.1820; found: 574.1817.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5-m-tolyl-1,3,4-oxadiazol-2-yl)acetamide **(B12)**. White solid, 35.96% yield, m.p.: 221–223 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.61 (s, 1H), 7.92 (s, 1H), 7.88 (d, $J=7.6$ Hz, 1H), 7.68 (d, $J=7.9$ Hz, 1H), 7.55 (s, 1H), 7.37 (t, $J=7.6$ Hz, 1H), 7.31 (d, $J=7.4$ Hz, 1H), 7.02 (d, $J=8.5$ Hz, 1H), 6.57 (s, 1H), 6.41 (s, 1H), 4.40 (s, 2H), 4.02 − 3.96 (m, 9H), 3.93 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 164.9, 161.6, 161.1, 159.0, 156.8, 154.5, 151.8, 149.3, 140.7, 138.7, 132.1, 128.7, 127.2, 123.9, 123.7, 122.2, 121.8, 111.3, 110.9, 108.5, 96.4, 92.7, 73.2, 56.6, 56.3, 56.1, 55.9, 21.3. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{28}N_3O_9$: 574.1820; found: 574.1816.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5-o-tolyl-1,3,4-oxadiazol-2-yl)acetamide **(B13)**. White solid, 49.04% yield, m.p.: 234–236 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.62 (s, 1H), 7.98 (d, $J=7.7$ Hz, 1H), 7.68 (dd, $J=8.4$, 1.3 Hz, 1H), 7.55 (s, 1H), 7.39 (t, $J=7.4$ Hz, 1H), 7.31 (dd, $J=16.6$, 8.0 Hz, 2H), 7.02 (d, $J=8.5$ Hz, 1H), 6.56 (d, $J=1.6$ Hz, 1H), 6.41 (d, $J=1.4$ Hz, 1H), 4.40 (s, 2H), 4.01–3.96 (m, 9H), 3.93 (s, 3H), 2.73 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.7, 164.9, 161.7, 161.1, 159.0, 156.7, 154.5, 151.8, 149.3, 140.7, 138.3, 131.5, 130.8, 128.9, 125.9, 123.0, 122.2, 121.9, 111.3, 110.9, 108.5, 96.4, 92.7, 73.2, 56.5, 56.3, 56.1, 55.9, 21.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{28}N_3O_9$: 574.1820; found: 574.1818.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B14)**. Light yellow solid, 36.20% yield, m.p.: 235–237 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.10 (s, 1H), 8.91 (s, 1H), 8.46 (d, $J=7.6$ Hz, 1H), 8.37 (d, $J=8.1$ Hz, 1H), 7.70 (dd, $J=18.7$, 8.6 Hz, 2H), 7.55 (s, 1H), 7.03 (d, $J=8.5$ Hz, 1H), 6.58 (s, 1H), 6.43 (s, 1H), 4.41 (s, 2H), 4.03 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.9, 166.8, 165.0, 161.1, 159.3, 159.1, 157.6, 154.7, 151.9, 149.3, 148.6, 140.8, 132.2, 130.2, 125.7, 125.6, 122.3, 121.7, 121.5, 111.3, 110.9, 108.4, 96.5, 92.7, 73.4, 56.6, 56.2, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}N_4O_{11}$: 605.1514; found: 605.1511.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(2-nitrophenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B15)**. Light yellow solid, 46.53% yield, m.p.: 254–256 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.18 (d, $J=8.0$ Hz, 1H), 8.00 (d, $J=7.5$ Hz, 1H), 7.95 (t, $J=7.5$ Hz, 1H), 7.91 (t, $J=7.6$ Hz, 1H), 7.75 (d, $J=8.1$ Hz, 2H), 7.12 (d, $J=8.4$ Hz, 1H), 6.87 (s, 1H), 6.52 (s, 1H), 4.80 (s, 2H), 3.91 (s, 3H), 3.87–3.82 (m, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.8, 167.2, 164.4, 160.8, 158.6, 158.3, 157.5, 152.3, 151.4, 148.9, 148.20, 139.4, 134.2, 133.7, 131.6, 125.3, 122.6, 122.2, 117.5, 112.0, 111.9, 108.5, 96.6, 93.6, 70.7, 56.6, 56.5, 56.1, 56.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}N_4O_{11}$: 605.1514; found: 605.1510.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B16)**. White solid, 41.83% yield, m.p.: 210–212 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.94 (s, 1H), 8.22 (d, $J=8.2$ Hz, 2H), 7.75 (d,

$J = 8.3$ Hz, 2H), 7.68 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.55 (d, $J = 2.0$ Hz, 1H), 7.02 (d, $J = 8.6$ Hz, 1H), 6.57 (d, $J = 2.2$ Hz, 1H), 6.42 (d, $J = 2.1$ Hz, 1H), 4.40 (s, 2H), 4.01 (s, 3H), 3.99 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 166.8, 164.9, 161.0, 160.2, 159.0, 157.5, 154.7, 151.9, 149.3, 140.8, 132.9, 127.1, 126.9 (2 C), 125.9 (2 C), 123.6, 122.3, 121.7, 111.3, 110.9, 108.4, 96.5, 92.7, 73.3, 56.6, 56.2, 56.1, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}F_3N_3O_9$: 628.1537; found: 628.1535.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B17)**. White solid, 50.80% yield, m.p.: 195–197 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.90 (s, 1H), 8.34 (s, 1H), 8.30 (d, $J = 7.7$ Hz, 1H), 7.76 (d, $J = 7.5$ Hz, 1H), 7.68 (d, $J = 8.5$ Hz, 1H), 7.64 (t, $J = 7.8$ Hz, 1H), 7.54 (s, 1H), 7.02 (d, $J = 8.5$ Hz, 1H), 6.57 (d, $J = 1.8$ Hz, 1H), 6.42 (s, 1H), 4.40 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 166.8, 165.0, 161.1, 160.1, 159.1, 157.4, 154.7, 151.9, 149.3, 140.8, 131.6, 129.8, 129.5, 127.8, 124.8, 123.6, 123.5, 122.3, 121.7, 111.3, 110.9, 108.4, 96.5, 92.7, 73.3, 56.5, 56.2, 56.1, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}F_3N_3O_9$: 628.1537; found: 628.1533.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(2-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B18)**. White solid, 58.25% yield, m.p.: 225–227 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.99 (s, 1H), 8.05 (d, $J = 7.3$ Hz, 1H), 7.85 (d, $J = 7.4$ Hz, 1H), 7.72–7.63 (m, 3H), 7.54 (s, 1H), 7.01 (d, $J = 8.6$ Hz, 1H), 6.55 (d, $J = 1.7$ Hz, 1H), 6.40 (d, $J = 1.6$ Hz, 1H), 4.39 (s, 2H), 4.00–3.95 (m, 9H), 3.92 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 166.7, 165.0, 161.3, 159.4, 159.1, 158.0, 154.6, 151.9, 149.4, 140.9, 131.9, 131.3, 129.2, 129.0, 126.9, 123.2, 122.6, 122.3, 121.9, 111.4, 111.1, 108.6, 96.5, 92.8, 73.4, 56.5, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}F_3N_3O_9$: 628.1537; found: 628.1537.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(4-(trifluoromethoxy)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B19)**. White solid, 54.40% yield, m.p.: 217–219 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.78 (s, 1H), 8.13 (d, $J = 8.7$ Hz, 2H), 7.68 (dd, $J = 8.5$, 1.8 Hz, 1H), 7.54 (d, $J = 1.6$ Hz, 1H), 7.33 (d, $J = 8.3$ Hz, 2H), 7.02 (d, $J = 8.6$ Hz, 1H), 6.57 (d, $J = 1.9$ Hz, 1H), 6.42 (d, $J = 1.9$ Hz, 1H), 4.39 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.8, 164.9, 161.0, 160.3, 159.0, 157.2, 154.6, 151.8, 151.3, 149.2, 140.7, 128.4 (2 C), 122.4, 122.2, 121.7, 121.1 (2 C), 120.3, 111.2, 110.9, 108.4, 96.4, 92.7, 73.2, 56.5, 56.2, 56.1, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}F_3N_3O_{10}$: 644.1487; found: 644.1484.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(3-(trifluoromethoxy)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B20)**. White solid, 38.85% yield, m.p.: 207–209 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.78 (s, 1H), 8.04 (d, $J = 7.7$ Hz, 1H), 7.94 (s, 1H), 7.70–7.65 (m, 1H), 7.57–7.51 (m, 2H), 7.36 (d, $J = 7.7$ Hz, 1H), 7.02 (d, $J = 8.5$ Hz, 1H), 6.57 (d, $J = 1.7$ Hz, 1H), 6.42 (d, $J = 1.6$ Hz, 1H), 4.40 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 164.9, 161.1, 160.1, 159.0, 157.3, 154.6, 151.9, 149.6, 149.4, 140.8, 130.5, 125.8, 124.9, 123.5, 122.2, 121.8, 120.4, 119.2, 111.4, 111.1, 108.5, 96.4, 92.8, 73.3, 56.5, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}F_3N_3O_{10}$: 644.1487; found: 644.1486.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(2-(trifluoromethoxy)phenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B21)**. White solid, 43.71% yield, m.p.: 226–228 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.82 (s, 1H), 8.16 (d, $J = 7.5$ Hz, 1H), 7.67 (d, $J = 8.1$ Hz, 1H), 7.59–7.52 (m, 2H), 7.48–7.40 (m, 2H), 7.01 (d, $J = 8.4$ Hz, 1H), 6.56 (s, 1H), 6.40 (s, 1H), 4.40 (s, 2H), 4.01–3.90 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.6, 164.9, 161.2, 159.0, 158.3, 157.6, 154.5, 151.9, 149.3, 146.4, 140.8, 132.4, 130.5, 127.2, 122.2, 122.1, 121.9, 120.5, 118.2, 111.3, 111.1, 108.5, 96.4, 92.7, 73.3, 56.4, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}F_3N_3O_{10}$: 644.1487; found: 644.1482.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B22)**. White solid, 44.52% yield, m.p.: 206–208 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.51 (s, 1H), 8.02 (d, $J = 8.7$ Hz, 2H), 7.67 (d, $J = 8.5$ Hz, 1H), 7.54 (s, 1H), 7.02 (d, $J = 8.5$ Hz, 1H), 6.98 (d, $J = 8.7$ Hz, 2H), 6.56 (s, 1H), 6.41 (s, 1H), 4.39 (s, 2H), 4.01–3.96 (m, 9H), 3.93 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.7, 164.9, 162.1, 161.5, 161.1, 159.0, 156.5, 154.5, 151.8, 149.3, 140.7, 128.5 (2 C), 122.2, 121.9, 116.5, 114.3 (2 C), 111.3, 110.9, 108.5, 96.4, 92.7, 73.2, 56.5, 56.3, 56.1, 55.9, 55.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{28}N_3O_{10}$: 590.1769; found: 590.1769.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5–(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl)acetamide **(B23)**. White solid, 47.70% yield, m.p.: 205–207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.67 (s, 1H), 7.70–7.64 (m, 2H), 7.63–7.60 (m, 1H), 7.54 (d, $J = 2.0$ Hz, 1H), 7.38 (t, $J = 8.0$ Hz, 1H), 7.07–7.03 (m, 1H), 7.01 (d, $J = 8.6$ Hz, 1H), 6.56 (d, $J = 2.2$ Hz, 1H), 6.41 (d, $J = 2.2$ Hz, 1H), 4.39 (s, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.8, 164.9, 161.4, 161.1, 159.9, 159.1, 156.9, 154.5, 151.8, 149.2, 140.7, 129.9, 124.9, 122.2, 121.8, 119.2, 118.1, 111.2, 111.1, 110.9, 108.4, 96.4, 92.7, 73.2, 56.6, 56.2, 56.1, 55.9, 55.5. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{28}N_3O_{10}$: 590.1769; found: 590.1764.

N-(5–(3-chloro-4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B24)**. White solid, 40.86% yield, m.p.: 232–234 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.85 (s, 1H), 8.16 (dd, $J = 6.9$, 2.0 Hz, 1H), 8.02–7.98 (m, 1H), 7.68 (dd, $J = 8.5$, 1.9 Hz, 1H), 7.54 (d, $J = 1.7$ Hz, 1H), 7.27 (t, $J = 8.6$ Hz, 2H), 7.02 (d, $J = 8.6$ Hz, 1H), 6.57 (d, $J = 2.1$ Hz, 1H), 6.42 (d, $J = 2.0$ Hz, 1H), 4.39 (s, 2H), 4.01 (s, 3H), 3.99 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 166.8, 164.9, 161.1, 160.1, 159.1, 159.0, 157.2, 154.7, 151.9, 149.3, 140.8, 129.1, 126.8, 122.3, 122.3, 121.8, 121.2, 117.3, 111.4, 110.9, 108.4, 96.5, 92.8, 73.3, 56.6, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{24}ClFN_3O_9$: 612.1180; found: 612.1180.

N-(5–(3,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B25)**. White solid, 35.80% yield, m.p.: 230–232 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.25 (s, 1H), 8.04 (s, 1H), 7.87 (s, 2H), 7.77–7.72 (m, 2H), 7.11 (d, $J = 8.4$ Hz, 1H), 6.85 (s, 1H), 6.51 (s, 1H), 4.80 (s, 2H), 3.90 (s, 3H), 3.88–3.84 (m, 6H), 3.83 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.8, 167.3, 164.5, 160.8, 159.3, 158.6, 157.9, 152.4, 151.5, 148.9, 139.4, 134.8, 132.7, 132.3, 127.9, 126.5, 124.3, 122.7, 122.2, 112.2, 111.9, 108.6, 96.6, 93.6, 70.9, 56.6, 56.5, 56.2, 56.1. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{24}Cl_2N_3O_9$: 628.0884; found: 628.0884.

N-(5–(3,5-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B26)**. White solid, 45.40% yield, m.p.: 200–202 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.52 (s, 1H), 7.67 (dd, $J = 8.5$, 1.9 Hz, 1H), 7.55 (d, $J = 1.8$ Hz, 1H), 7.23 (d, $J = 2.2$ Hz, 2H), 7.01 (d, $J = 8.6$ Hz, 1H), 6.59 (t, $J = 2.2$ Hz, 1H), 6.56 (d, $J = 2.1$ Hz, 1H), 6.41 (d, $J = 2.0$ Hz, 1H), 4.40 (s, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 3.85 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.7, 164.9, 161.5, 161.1, 161.1 (2 C), 159.0, 156.9, 154.5, 151.8, 149.3, 140.7, 125.4, 122.2, 121.8, 111.3, 110.9, 108.5, 104.5 (2 C), 104.3, 96.4, 92.7, 73.2, 56.5, 56.3, 56.1, 55.9, 55.6 (2 C). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{30}N_3O_{11}$: 620.1875; found: 620.1873.

N-(5–(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide

(B27). White solid, 42.37% yield, m.p.: 151–153 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.62 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.59 (s, 1H), 7.54 (s, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.55 (s, 1H), 6.40 (s, 1H), 4.38 (s, 2H), 4.01–3.90 (m, 18H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.8, 164.9, 161.6, 161.1, 159.0, 156.6, 154.6, 151.9, 151.8, 149.3(2 C), 140.7, 122.2, 121.8, 120.3, 116.5, 111.3, 111.1, 111.0, 109.4, 108.5, 96.4, 92.8, 73.2, 56.5, 56.3, 56.2, 56.1, 55.9, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{30}N_3O_{11}$: 620.1875; found: 620.1872.

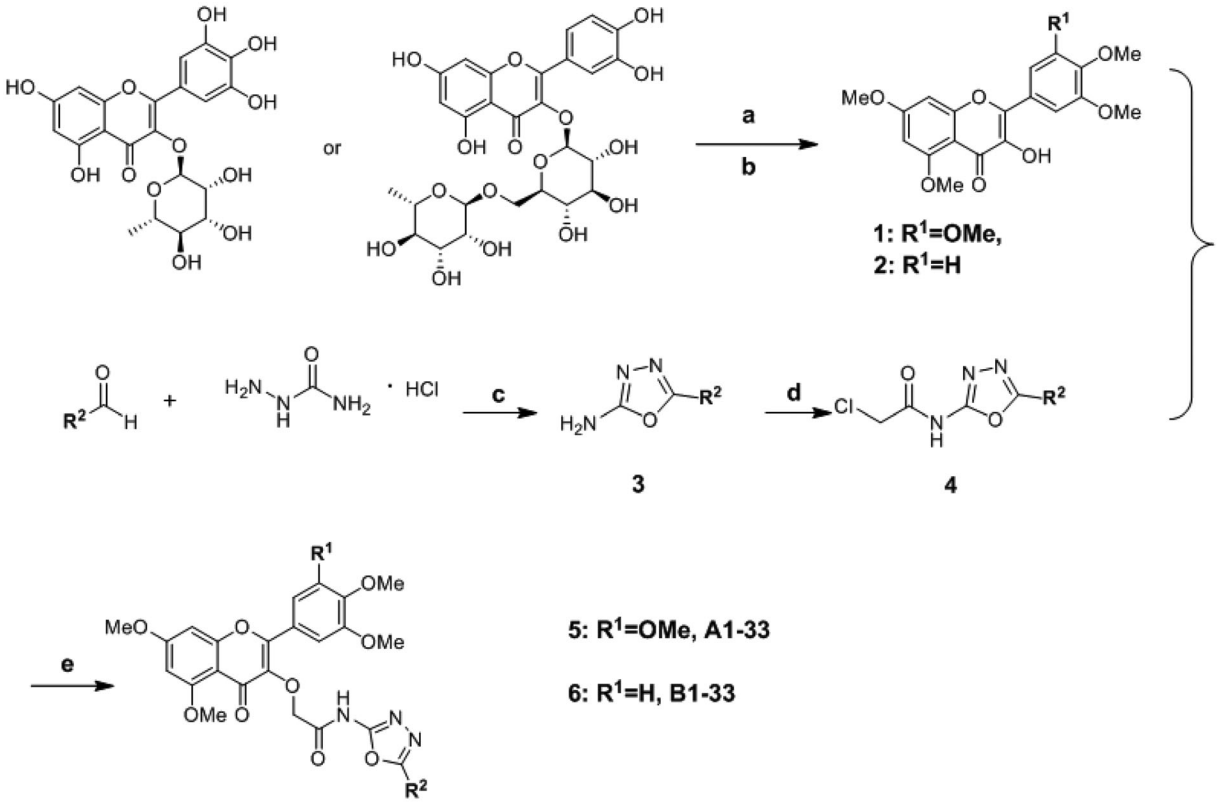
2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5-(naphthalen-1-yl)-1,3,4-oxadiazol-2-yl)acetamide **(B28)**. White solid, 51.26% yield, m.p.: 230–232 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.64 (s, 1H), 9.28 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 7.1 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.9 Hz, 2H), 7.61–7.53 (m, 3H), 7.02 (d, J = 8.5 Hz, 1H), 6.56 (s, 1H), 6.41 (s, 1H), 4.44 (s, 2H), 4.03–3.96 (m, 9H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.8, 164.9, 161.6, 161.2, 159.1, 156.8, 154.5, 151.9, 149.4, 140.8, 133.9, 132.2, 130.1, 128.5, 128.3, 128.1, 126.6, 126.5, 124.9, 122.3, 121.9, 120.5, 111.4, 111.2, 108.6, 96.5, 92.8, 73.3, 56.6, 56.4, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{28}N_3O_9$: 610.1820; found: 610.1817.

N-(5–(2,3-dihydrobenzo[b][1, 4]dioxin-6-yl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B29)**. White solid, 50.60% yield, m.p.: 228–230 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.45 (s, 1H), 7.67 (dd, J = 8.5, 1.6 Hz, 1H), 7.60 (d, J = 1.6 Hz, 1H), 7.57 (dd, J = 8.5, 1.6 Hz, 1H), 7.55 (s, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 1.8 Hz, 1H), 6.41 (d, J = 1.7 Hz, 1H), 4.39 (s, 2H), 4.30 (dd, J = 12.1, 5.0 Hz, 4H), 3.99 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.7, 164.9, 161.3, 161.1, 159.0, 156.5, 154.5, 151.9, 149.3, 146.4, 143.8, 140.7, 122.2, 121.9, 120.4, 117.8, 117.2, 115.9, 111.3, 111.0, 108.5, 96.4, 92.7, 73.2, 64.6, 64.2, 56.5, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}N_3O_{11}$: 618.1718; found: 618.1715.

N-(5–(3-(benzyloxy)phenyl)-1,3,4-oxadiazol-2-yl)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)acetamide **(B30)**. White solid, 47.88% yield, m.p.: 156–158 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.58 (s, 1H), 7.72 (s, 1H), 7.70–7.65 (m, 2H), 7.55 (d, J = 1.5 Hz, 1H), 7.46 (d, J = 7.3 Hz, 2H), 7.39 (t, J = 7.4 Hz, 3H), 7.33 (t, J = 7.2 Hz, 1H), 7.11 (dd, J = 8.1, 1.7 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.56 (d, J = 1.9 Hz, 1H), 6.40 (d, J = 1.8 Hz, 1H), 5.14 (s, 2H), 4.40 (s, 2H), 4.00–3.90 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 164.9, 161.4, 161.1, 159.1, 159.0, 156.9, 154.5, 151.9, 149.3, 140.7, 136.5, 130.1, 128.6 (2 C), 128.1, 127.6 (2 C), 125.0, 122.2, 121.8, 119.4, 118.6, 112.3, 111.3, 110.9, 108.5, 96.4, 92.7, 73.2, 70.3, 56.5, 56.2, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{32}N_3O_{10}$: 666.2082; found: 666.2079.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)acetamide **(B31)**. White solid, 47.78% yield, m.p.: 233–235 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.73 (s, 1H), 7.67 (dd, J = 8.5, 1.9 Hz, 1H), 7.61 (d, J = 0.9 Hz, 1H), 7.54 (d, J = 1.7 Hz, 1H), 7.16 (d, J = 2.9 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.58–6.57 (m, 1H), 6.57 (d, J = 2.2 Hz, 1H), 6.41 (d, J = 1.9 Hz, 1H), 4.39 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.7, 164.9, 161.1, 159.0, 156.4, 154.6, 154.3, 151.8, 149.3, 145.3, 140.8, 139.3, 122.2, 121.8, 113.5, 111.9, 111.3, 110.9, 108.4, 96.4, 92.7, 73.2, 56.6, 56.2, 56.1, 55.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}N_3O_{10}$: 550.1456; found: 550.1457.

2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5-(thiophen-2-yl)-1,3,4-oxadiazol-2-yl)acetamide **(B32)**. White solid, 49.73% yield, m.p.: 238–240 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.54 (s, 1H), 7.78 (d, J = 2.7 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.15 (t, J = 4.2 Hz, 1H),



Scheme 1. Synthesis of title compounds **A1–A33** and **B1–B33**. Reagent and conditions: (**a**) K_2CO_3, $(CH_3)_2SO_4$, acetone, reflux, 48 h; (**b**) Conc.HCl, EtOH, reflux, 2 h; (**c**) AcONa, MeOH/H_2O, rt, K_2CO_3, I_2, 1,4-dioxane, 85 °C, 5 h; (**d**) Chloroacetyl chloride, DMF, rt, 12 h; (**e**) K_2CO_3, KI, acetone, reflux, overnight.

7.02 (d, $J = 8.5$ Hz, 1H), 6.57 (s, 1H), 6.42 (s, 1H), 4.40 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.6, 166.7, 164.9, 161.2, 159.0, 157.9, 156.3, 154.5, 151.9, 149.4, 140.7, 129.5, 129.4, 127.8, 125.3, 122.2, 121.9, 111.4, 111.1, 108.6, 96.4, 92.8, 73.2, 56.5, 56.3, 56.1, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}N_3O_9S$: 566.1228; found: 566.1227.

(E)-2–(2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4-oxo-4H-chromen-3-yloxy)-N-(5-styryl-1,3,4-oxadiazol-2-yl)acetamide **(B33)**. White solid, 42.70% yield, m.p.: 226–228 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.64 (s, 1H), 7.70–7.65 (m, 1H), 7.60–7.52 (m, 4H), 7.43–7.34 (m, 3H), 7.03 (d, $J = 2.4$ Hz, 1H), 7.01 (d, $J = 5.1$ Hz, 1H), 6.57 (d, $J = 1.9$ Hz, 1H), 6.41 (d, $J = 1.8$ Hz, 1H), 4.39 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 166.6, 164.9, 161.1, 161.1, 159.1, 156.4, 154.6, 151.9, 149.3, 140.8, 138.1, 135.0, 129.6, 128.9, 127.4, 122.2, 121.8, 111.3, 110.9, 109.9, 108.5, 96.4, 92.8, 73.3, 56.6, 56.2, 56.1, 55.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{28}N_3O_9$: 586.1820; found: 586.1816.

2.3. Telomerase activity assay[23]

2.4. Cell culture

A375, MDA-MB-231, MGC-803, SMMC-7721, SGC-7901 and L-02 cell lines were cultured in DMEM medium supplemented with 10% (V/V) heat-inactivated fetal bovine serum (FBS) (Biological Industries, Israel) along with 100 U/mL penicillin and 100 mg/mL streptomycin (Beyotime, China). Cells were grown in a humidified 5% CO_2 atmosphere at 37 °C and maintained in a logarithmic growth phase for all experiments.

2.5. Anticancer assay[23]

2.6. Cell cycle assay

For cell cycle analysis, cell cycle kit (Beyotime, China) was performed. MGC-803 cells were treated with compound **A33** at different concentrations for 48 h. Untreated and treated cells were harvested, and then MGC-803 cells were washed three times using cold PBS. And then cells were fixed in 70% ethanol at −20 °C for

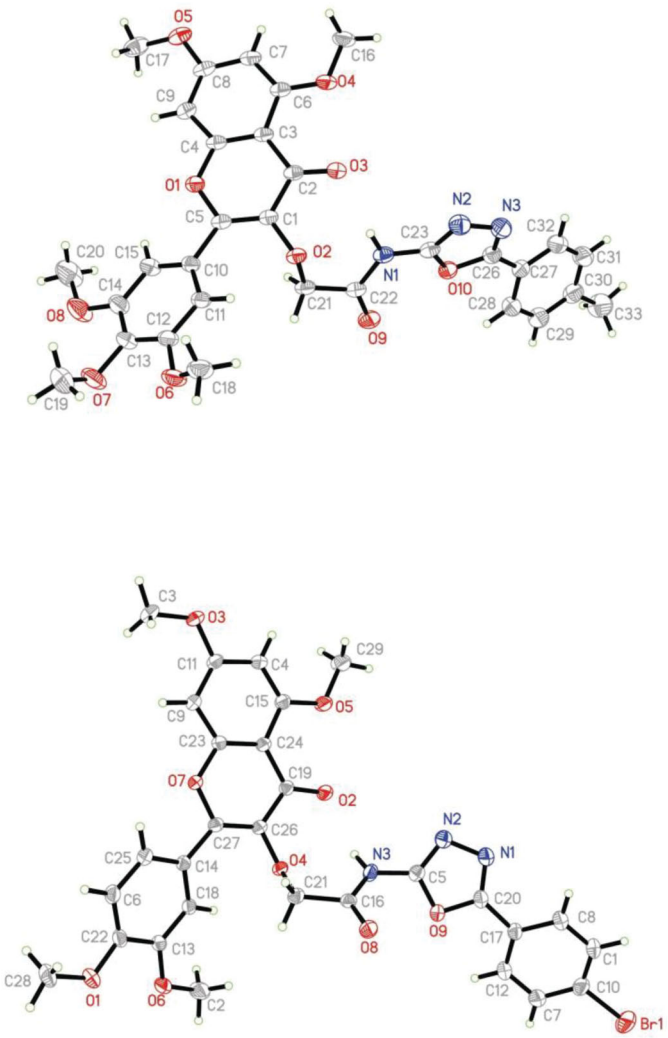
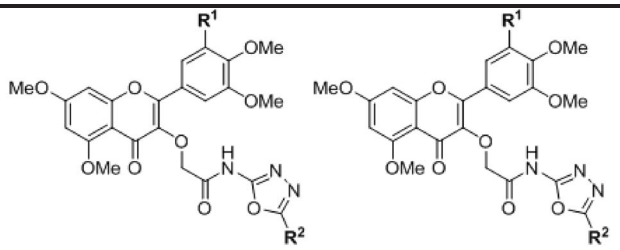


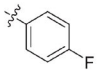
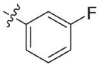
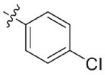
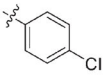
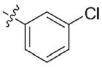
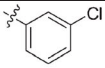
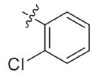
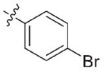
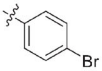
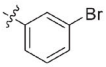
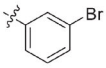
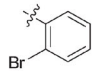
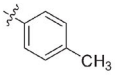
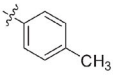
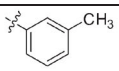
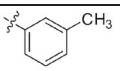
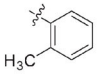
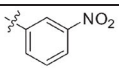
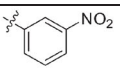
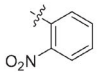
Figure 2. ORTEP drawing of compounds **A11** and **B8**.

Table 1. Crystallographical and experimental data of compounds **A11** and **B8**.

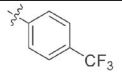
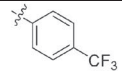
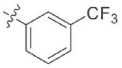
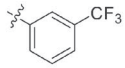
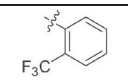
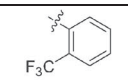
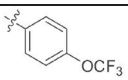
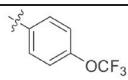
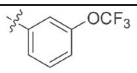
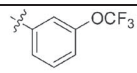
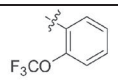
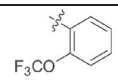
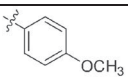
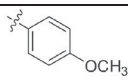
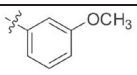
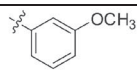
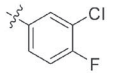
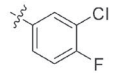
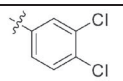
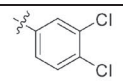
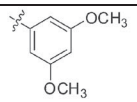
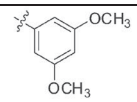
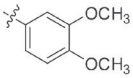
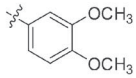
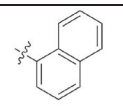
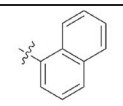
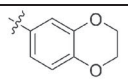
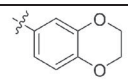
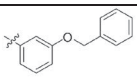
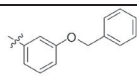
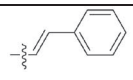
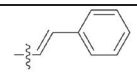
Properties	A11	B8
Chemical formula	$C_{31}H_{29}N_3O_{10}$	$C_{29}H_{24}BrN_3O_9$
Formula weight	603.57	638.42
Temperature/K	292.56(16)	293(2)
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$
a/Å	20.5711(10)	11.1453(2)
b/Å	7.5520(3)	29.8454(7)
c/Å	20.9843(11)	8.3870(3)
α/°	90	90
β/°	116.413(6)	101.156(3)
γ/°	90	90
Volume/Å^3	2919.7(3)	2737.11(12)
Z	4	4
ρ_{calc}g/cm^3	1.369	1.549
μ/mm^1	0.849	1.564
F(000)	1264.0	1304.0
Crystal size/mm^3	0.17 × 0.04 × 0.02	0.25 × 0.22 × 0.19
2Θ range for data collection/°	8.078 to 133.186	3.72–52
Index ranges		
Reflections collected	11523	22575
Data/restraints/parameters	5029/0/403	5385/0/379
Goodness-of-fit on F^2	1.036	1.012
Final R indexes [$I \geq 2\sigma$ (I)]	$R_1 = 0.0529$, $wR_2 = 0.1381$	$R_1 = 0.0472$, $wR_2 = 0.1039$
Final R indexes [all data]	$R_1 = 0.0739$, $wR_2 = 0.1577$	$R_1 = 0.0705$, $wR_2 = 0.1137$
Largest diff. peak/hole/e Å^{-3}	0.25/−0.23	0.62/−0.69

Table 2. Chemical structures of compounds **A1–A33** and **B1–B33** and inhibitory activity on telomerase.



Compds	R^1	R^2	Telomerase[a] IC_{50}(μM)	Compds	R^1	R^2	Telomerase[a] IC_{50}(μM)
A1	OCH_3		21.11±2.28	**B1**	H		-[b]
A2	OCH_3		0.77±0.13	**B2**	H		1.38±0.25
A3	OCH_3		2.57±0.50	**B3**	H		4.30±0.77
A4	OCH_3		12.13±2.01	**B4**	H		15.30±2.71
A5	OCH_3		0.81±0.13	**B5**	H		4.22±0.62
A6	OCH_3		7.35±1.01	**B6**	H		15.44±4.20
A7	OCH_3		12.52±1.88	**B7**	H		24.33±2.70
A8	OCH_3		1.22±0.29	**B8**	H		4.29±0.83
A9	OCH_3		2.01±0.39	**B9**	H		2.90±0.45
A10	OCH_3		21.05±4.09	**B10**	H		-
A11	OCH_3		2.35±0.48	**B11**	H		5.65±1.77
A12	OCH_3		15.33±2.85	**B12**	H		-
A13	OCH_3		25.08±2.01	**B13**	H		8.09±2.25
A14	OCH_3		4.11±0.60	**B14**	H		8.29±1.33
A15	OCH_3		6.98±0.96	**B15**	H		17.20±2.98

(*continued*)

A16	OCH_3		0.62±0.11	**B16**	H		1.29±0.20
A17	OCH_3		4.11±0.62	**B17**	H		27.55±3.11
A18	OCH_3		1.07±0.20	**B18**	H		2.79±0.55
A19	OCH_3		1.21±0.29	**B19**	H		1.77±0.60
A20	OCH_3		0.92±0.17	**B20**	H		20.01±1.96
A21	OCH_3		5.11±1.10	**B21**	H		9.22±1.01
A22	OCH_3		9.11±1.88	**B22**	H		14.29±1.33
A23	OCH_3		1.90±0.42	**B23**	H		2.44±0.42
A24	OCH_3		4.01±0.47	**B24**	H		4.17±0.70
A25	OCH_3		-	**B25**	H		-
A26	OCH_3		1.06±0.11	**B26**	H		3.99±0.85
A27	OCH_3		0.32±0.07	**B27**	H		0.51±0.10
A28	OCH_3		6.17±0.99	**B28**	H		1.19±0.18
A29	OCH_3		-	**B29**	H		2.98±0.27
A30	OCH_3		-	**B30**	H		-
A31	OCH_3		2.75±0.19	**B31**	H		2.82±0.25
A32	OCH_3		2.22±0.51	**B32**	H		3.75±0.39
A33	OCH_3		0.44±0.09	**B33**	H		0.97±0.20
Staurosporine[c]			6.41±1.38	**BIBR1532**[c]			0.29±0.06

[a] Telomerase supercoiling activity.
[b] No activity was observed in the concentration range of 0-60 μM.
[c] Staurosporine and BIBR1532 were reported as a control.

1 h. After fixation, cells were washed with cold PBS and stained with 0.5 ml of propidium iodide (PI) staining buffer, which contain 200 mg/mL RNase A and 50 μg/mL PI, at 37 °C for 30 min in the dark. Analyses were conducted on FACSVerse Flow Cytometer (Becton Dickinson). The experiments were repeated three times.

2.7. Apoptosis assay

For cell apoptosis analysis, we employed annexin V-FITC/PI apoptosis detection kit (BestBio, China). MGC-803 cells in logarithmic growth phase were treated with compound **A33** at different concentrations for 48 h. Cells were collected in cold PBS by centrifugation for 5 min at 1000 g. And then cells were re-suspended at a buffer (1×10^6 cells/mL), stained with FITC-labeled annexin V and PI for 20 min in the dark and immediately analysed on FACSVerse Flow Cytometer (Becton Dickinson).

2.8. Western blotting

Human MGC-803 cells were lysed with RIPA lysis buffer (Beyotime, China). Whole extracts were prepared, and protein concentration was detected using a BCA protein assay kit (Beyotime, China). The protein samples were separated by SDS-PAGE and blotted onto a PVDF membrane (Millipore Corp, Billerica, MA). After blockade of non-specific protein binding, nitrocellulose blots were incubated at 4 °C for 8 h with primary antibodies. After extensive washing in TBS/Tween-20, the membranes were incubated at room temperature for 1 h with secondary antibodies. After washed in TBS/Tween-20, the blots were processed with distilled water for detection of antigen using the enhanced chemiluminescence system. Proteins were visualised with ECL-chemiluminescent kit (ECL-plus, Thermo Scientific).

2.9. Statistical analysis

All data are expressed as means ± SD. Student's *t*-test was used to determine statistical significance at $p < 0.05$. SPSS 17.0 and Graphpad Prism 5 software were used for the statistical analyses.

3. Results and discussion

3.1. Chemistry

Myricitrin and Rutin are used as raw materials. The hydroxyl groups on the benzene ring were protected by methylation with dimethyl sulphate, and the glycosides were removed under strong acidic and reflux conditions to obtain 3-hydroxy-5,7-dimethoxy-2–(3,4,5-trimethoxyphenyl)-4H-chromen-4-one (**1**)[22] and 2–(3,4-dimethoxyphenyl)-3-hydroxy-5,7-dimethoxy-4H-chromen-4-one (**2**)[34], respectively. Secondly, a series of 5-substituted-1,3,4-oxadiazol-2-amines (**3**) were synthesised by the condensation of semicarbazide hydrochloride and the corresponding aldehydes and following by I_2**4**)[35] were prepared from reacting of the intermediate **3** with chloroethyl acid chloride in the presence of anhydrous DMF. Finally, title compounds, 2-phenyl-4H-chromone derivatives containing 1,3,4-oxadiazole and amide moieties, were synthesised by refluxing the key intermediate **1** with **4** in the presence of K_2CO_3 and KI in acetone. The synthetic route of title compounds **A1-A33** and **B1-B33** was showed in Scheme 1. All title compounds were characterised by means of ^{1}H NMR, ^{13}C NMR and HR-MS spectral analysis.

3.2. Crystal structure analysis

The structure of compounds **A11** and **B8** was further determined by X-ray crystallography. The crystal data were presented in Table 1. The molecular structure of compounds **A11** and **B8** was showed in Figure 2, respectively. Crystallographic data (excluding structure factors) for the structure had been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 2010105 and 2005763.

3.3. Telomerase inhibitory activity and SAR

All title compounds were assayed for telomerase activity using MGC-803 cells extract, Staurosporine and BIBR1532 used as the references[23]. The results were presented as mean ± SD, summarised in Table 2. Most of the title compounds demonstrated potent inhibition against telomerase. Among these, compounds **A2**, **A5**, **A16**, **A20**, **A27**, **A33**, **B27** and **B33** displayed significant inhibitory activity ($IC_{50} < 1$ μM), with IC_{50} values of 0.77, 0.81, 0.62, 0.92, 0.32, 0.44, 0.51 and 0.97 μM, respectively, which were found to be obviously superior to staurosporine ($IC_{50} = 6.41$ μM), and were comparable to BIBR1532 ($IC_{50} = 0.29$ μM). Moreover, these compounds have stronger telomerase inhibitory effect than the myricetin[22] and 1,3,4-oxadiazole[33] derivatives we reported previously.

Based on the data of Table 2, the preliminary SARs analysis revealed that except compounds **A13**, **A25**, **A28**, **A29** and **A30**, other compounds of **A** series ($\mathbf{R^1} = OCH_3$) possessed higher telomerase inhibitory activity than **B** series ($\mathbf{R^1}$ = H). Therefore, it

Table 3. Antiproliferative activity in *vitro* of compounds with strong telomerase inhibitory activity (IC_{50}<1 μM) against A375, MDA-MB-231, MGC-803, SMMC-7721 and SGC-7901 cell lines[a].

	IC_{50} (μM)[b]				
Compounds	A375	MDA-MB-231	MGC-803	SMMC-7721	SGC-7901
A2	11.03 ± 1.54	25.06 ± 2.10	17.26 ± 2.21	8.07 ± 1.30	56.91 ± 1.24
A5	20.09 ± 0.62	–[c]	15.22 ± 0.41	–	25.36 ± 0.59
A16	10.09 ± 0.52	–	–	–	–
A20	8.92 ± 0.69	19.50 ± 1.00	6.29 ± 0.36	–	10.22 ± 0.65
A27	–	–	–	–	–
A33	11.21 ± 0.69	9.89 ± 0.44	8.76 ± 0.25	9.67 ± 0.82	10.01 ± 0.51
B27	–	–	–	–	–
B33	–	–	–	–	–
BIBR1532[d]	57.58 ± 0.21	–	–	–	–
ADM[d]	0.58 ± 0.20	0.51 ± 0.12	0.42 ± 0.08	0.79 ± 0.13	0.82 ± 0.43

Negative control 0.1% DMSO, no activity.
[a]The data represented the mean of three experiments in triplicate and were expressed as means ± SD.
[b]The IC_{50} value was defined as the concentration at which 50% survival of cells was observed. The results are listed in the table.
[c]Not observed in the tested concentration range (>100 μM).
[d]Used as a positive control.

Table 4. Toxicity of compounds with strong telomerase inhibitory activity (IC_{50} < 1 μM) against human normal liver cells L-02[a].

Compounds	L-02 (IC_{50}, mM)
A2	1.37 ± 0.43
A5	1.99 ± 0.13
A16	0.90 ± 0.11
A20	0.62 ± 0.24
A27	1.38 ± 0.21
A33	2.21 ± 0.17
B27	1.67 ± 0.25
B33	1.01 ± 0.14

[a]MTT assays were used for evaluation, and values were expressed as mean IC_{50} of the triplicate experiment.

could be seen that the methoxy group (OCH_3) as a substituent at the R^1 position played a vital role in telomerase inhibitory activity.

The position, type and number of the substituents on the phenyl ring at R^2 and electronic effect had significant effects on inhibition of telomerase. Firstly, by comparing compounds **A2**–**A10**, when the phenyl ring at R^2 was substituted with halogen (F, Cl, Br), the inhibitory activity was *para* > *meta* > *ortho*. In addition, the substitution of halogen in the *para* and *ortho* position at the phenyl ring increased the activity with the increase of electronegativity (F > Cl > Br). A similar trend was also observed by comparing compounds **B2**-**B7**, **B8**, **B10**. Furthermore, compounds **A24**, **A25**, **B24** and **B25** disubstituted in the *para* and *meta* position at the phenyl ring demonstrated significant reduction or even complete loss of inhibitory activity as compared to the *para*-substituted compounds **A2**, **A5**, **B2** and **B5**. Secondly, by comparing compounds **A2-A21**, it was found that compounds with electron-withdrawing groups (F, Cl, Br, NO_2, CF_3, OCF_3) on the phenyl ring at R^2 displayed higher inhibitory activity than those with electron-donating groups (CH_3).

Interestingly, as compared to compounds **A22** and **A23**, compounds **A26** and **A27** bearing two the methoxy groups on the phenyl ring at R^2 exhibited stronger activity. A similar trend was also observed at compounds **B22**, **B23**, **B26** and **B27**. However, compounds **A30** and **B30** with a benzyl group at the *meta* position of the phenyl ring at R^2 completely lost inhibitory activity, which might be affected by steric hindrance. Finally, we found that replacement of the phenyl group at R^2 with aromatic fused rings and different aromatic heterocycles was also greatly important for activity.

As compared to compound **A1**, compounds **A28**, **A31**, **A32** substituted by naphthalene ring, furan ring and thiophene ring at R^2, respectively, displayed more potent inhibitory activity. A similar trend was also observed by comparing compounds **B1**, **B28**, **B31** and **B32**. In particular, replacement of the phenyl group at R^2 with styryl yielded compound **A33** and **B33**, which significantly increased inhibitory activity as compared to compounds **A1** and **B1**. It can be seen that styryl is crucial for activity and should be further optimised in the future study.

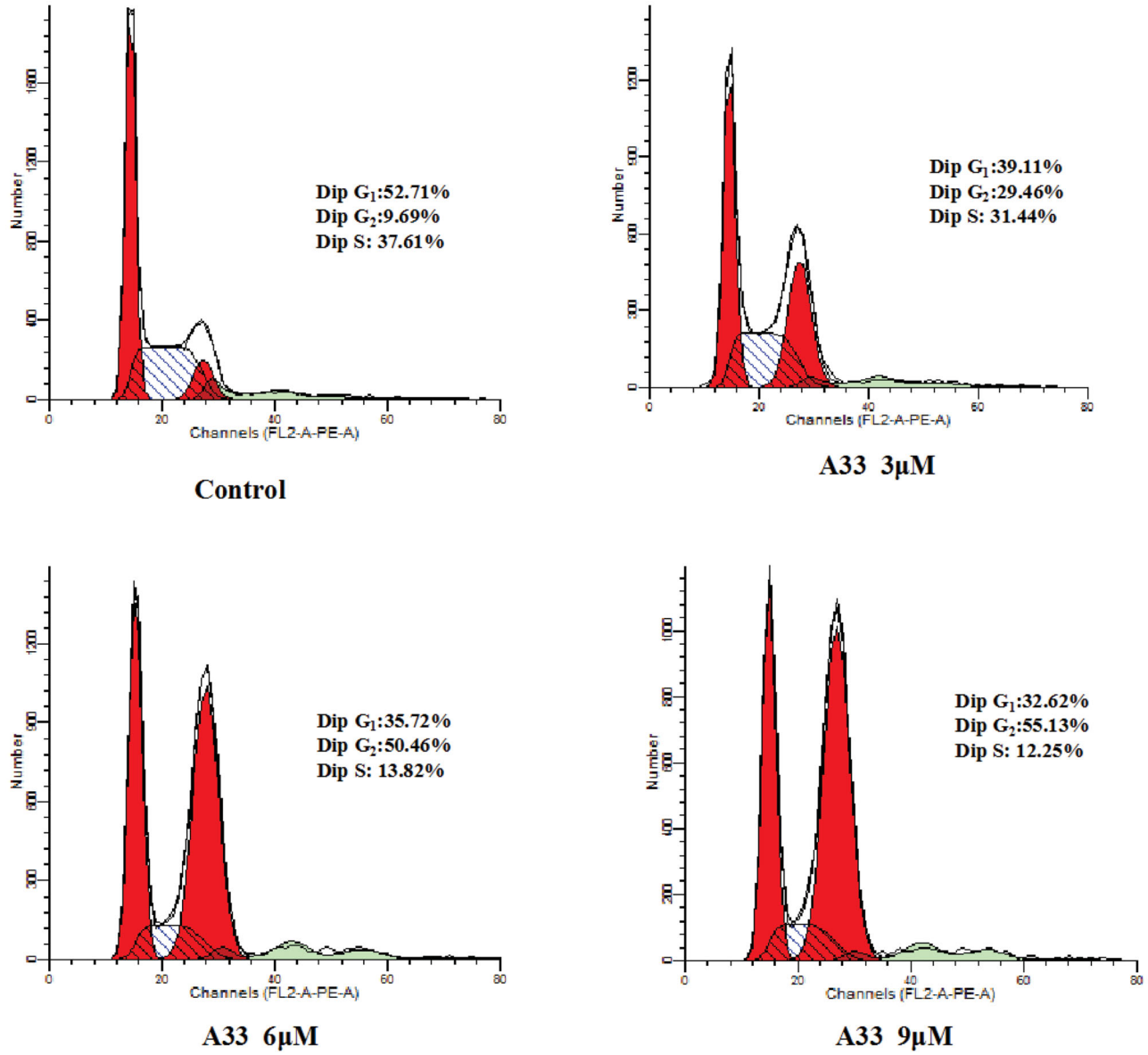


Figure 3. Cell cycle distribution induced by compound **A33** was measured in MGC-803 cells. Cells were treated with compound **A33** of 3, 6 and 9 μM for 48 h. Samples were analysed by flow cytometry and received results were analysed by modifit software.

3.4. In vitro anticancer activity

The most active compounds **A2**, **A5**, **A16**, **A20**, **A27**, **A33**, **B27** and **B33** ($IC_{50} < 1\,\mu M$) were selected to screen their *in vitro* anticancer activity against A375 (human melanoma cell), MDA-MB-231 (human breast cancer cell), MGC-803 (human gastric cancer cell), SMMC-7721 (human hepatoma cell) and SGC-7901 (human gastric cancer cell) cell lines using MTT assay. Adriamycin (ADM) and BIBR1532 were used as the references[22]. The IC_{50} values were summarised in Table 3. In general, similar to the telomerase inhibitor BIBR1532, most of compounds possessed excellent telomerase inhibitory activity but no obvious antiproliferative activity against solid cancer cells (**A5**, **A16**, **A27**, **B27**, **B33**). However, many title compounds exhibited moderate antiproliferative activity on human melanoma A375 cells (**A2**, **A5**, **A16**, **A20**, **A33**), which may be due to the high expression of telomerase in human melanoma A375 cells[36]. Besides, what should be of most concern was that compound **A33** with styryl, which demonstrated moderately effective antiproliferative activity against all tested five cancer cell lines as compared to other compounds. The results suggest that compound **A33** may have different mechanisms from BIBR1532 in inhibiting telomerase activity, which supports that this compound deserves further study.

3.5. Assay of human normal cell

In order to determine the selective cytotoxicity of selected compounds, we subsequently conducted a proliferative inhibition assay with human normal liver cell (L-02). The results were summarised in Table 4. It was observed that the selected eight title compounds all showed lower cytotoxicity. In particular, compound **A33** manifested an obvious non-toxic effect on L-02, with IC_{50} of 2.21 mM. The data indicated that compound **A33** displayed excellent selectivity against tumour cells over the normal somatic cells. Moreover, this compound exhibited lower cytotoxicity than 1,3,4-oxadiazole derivatives reported previously[33]. Therefore, in

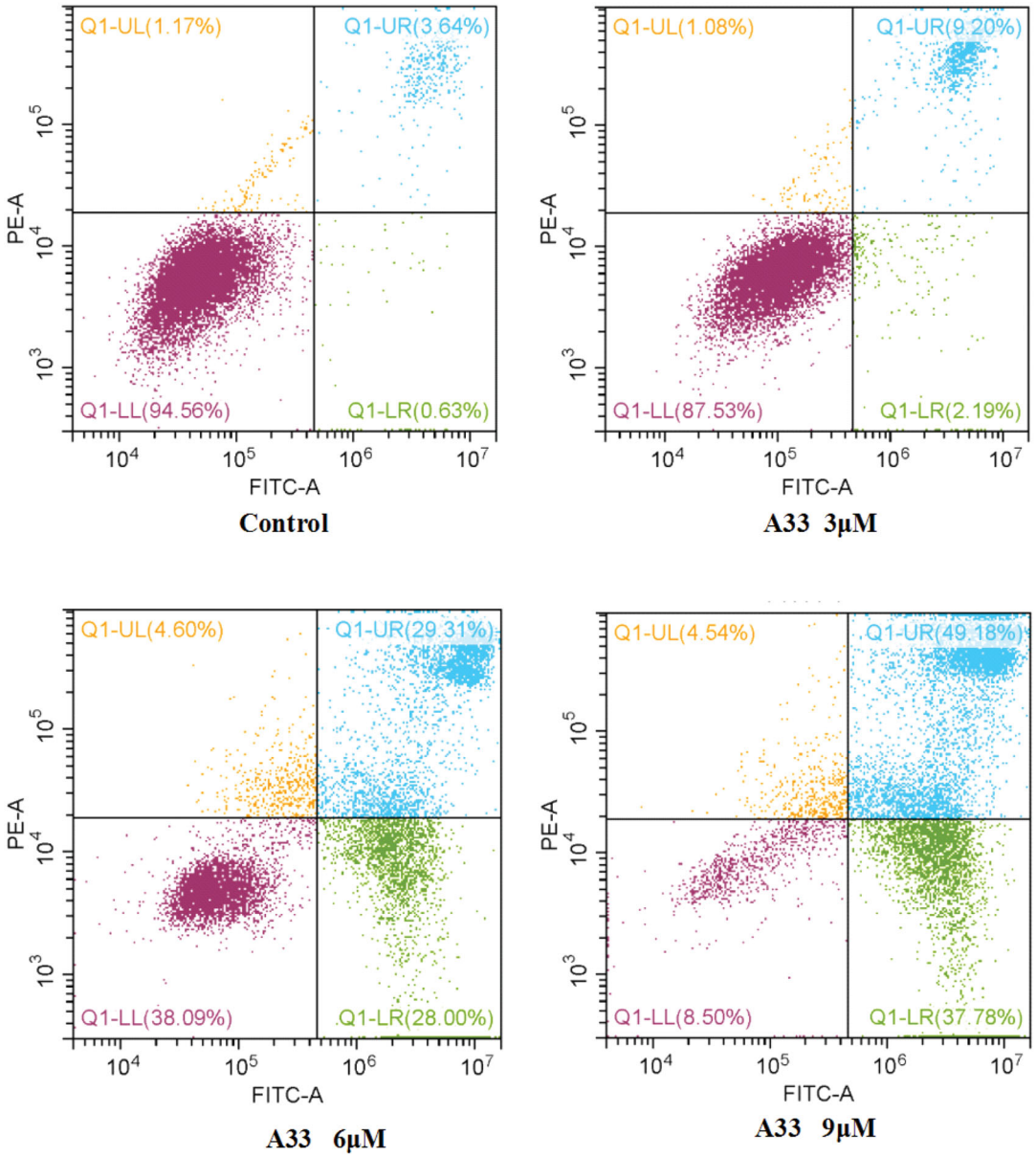


Figure 4. Percentage of apoptotic cells was determined in MGC-803 cells by Annexin-V FITC/PI staining. MGC-803 cells were treated with increasing concentrations of compound **A33** for 48 h and stained with Annexin-V FITC/PI. Apoptotic ratio increased, accompanied with the increase of concentration.

combination with the above points, it is quite meaningful to further explore the mechanisms of this compound.

3.6. Cell cycle analysis

The results of anticancer activity showed that compound **A33** could inhibit proliferation of MGC-803 cells. To verify whether cell cycle arrest leads to decrease cells proliferation, we used flow cytometric analysis to measure the effect of this compound on induction of cell cycle. As shown in Figure 3, treatment of MGC-803 cells with increasing concentrations (3, 6, 9 μM) of compound **A33** for 48 h, increased the G2/M phase distribution by 45.37% (from 9.76 to 55.13%), whereas the G0/G1 and S phase distribution decreased from 52.71 to 32.62% and from 37.61 to 12.25% in MGC-803 cells, respectively. In a word, this compound can induce cell cycle arrest at G2/M phase in a concentration-dependent manner, delaying cell cycle progression, thereby resulting in cell proliferation inhibition.

3.7. Cell apoptosis analysis

To determine whether compound **A33** meditated inhibition of proliferation was related with apoptosis, MGC-803 cells was selected for examination. The Annexin V-FITC/PI apoptosis detection kit was used in cell apoptosis analysis. As shown in Figure 4, the first quadrant usually represents damaged cells which was induced by mechanical forces, environmental stimulus and so on; the second quadrant generally denotes later period apoptotic cells and necrotic cells; the third quadrant often represents early apoptotic cells; and the fourth quadrant customarily denotes normal cells. The percentage of AnnexinV-FITC binding MGC-803 cells significantly increased from 4.27% to 11.39, 57.31 and 86.96%, respectively, after 48 h of treatment with increasing concentrations of compound **A33**. The results show that compound **A33** can induce apoptosis of MGC-803 cells in a concentration-dependent manner. This is consistent with the fact that telomerase inhibitors can induce apoptosis and thus inhibit the unlimited proliferation of tumour cells[37].

3.8. Down-regulated expression of Dyskerin-NOP10-NHP2

Dyskerin-NOP10-NHP2, trimer proteins are the core components of telomerase, playing a key role in the stabilisation, activation and assembly of telomerase, and the loss of dyskerin function can influence telomerase activity. Dyskerin over-expression associated with a variety of tumour types has been reported[38]. To test whether compound **A33** can modulate the expression of the trimer proteins, we used Western blotting. As shown in Figure 5, treatment with different concentrations (3, 6, 9 μM) of compound **A33** for 48 h (MGC-803 cells were selected), expression level of dyskerin protein was reduced in a concentration-dependent manner. Meanwhile, NHP2[39] and NOP10[40], as the important

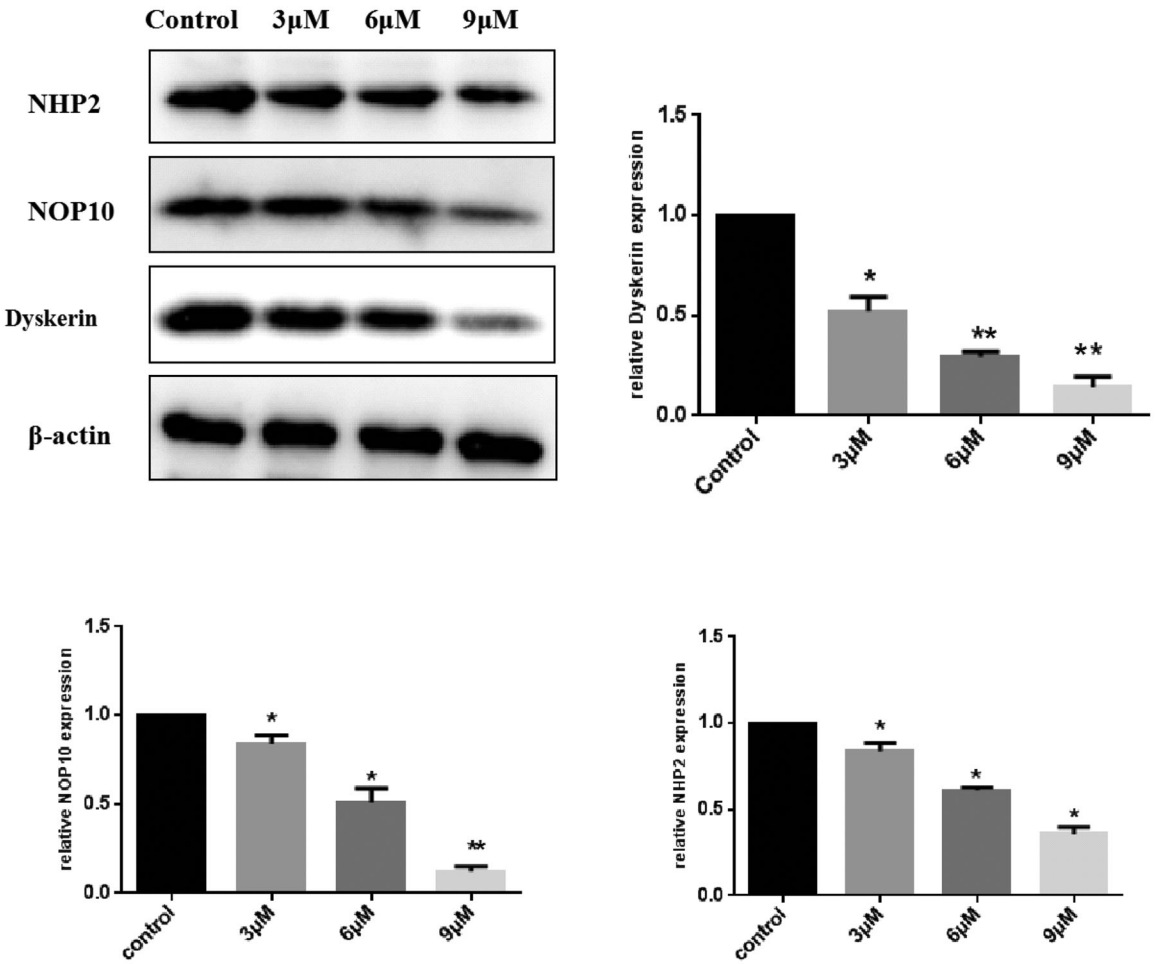


Figure 5. Compound **A33** inhibited Dyskerin expression in MGC-803 cells. MGC-803 cells were treated with compound **A33** of 3, 6 and 9 μM for 48 h. The proteins expression of Dyskerin, NOP10 and NHP2 were analysed by Western blotting. The results are expressed as relative expression against control expression. $n = 3$. Results are shown as mean ± SD from three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$.

components of dyskerin-NHP2-NOP10 trimer, had also been assessed together. The results indicated that expressions of NOP10 and NHP2 were also lower level than control group. Therefore, compound **A33** may be an efficient dyskerin regulator.

4. Conclusions

With the aim to discover highly efficient telomerase inhibitors, upon extensive optimisation, a total of 66 2-phenyl-4H-chromone derivatives containing amide and 1,3,4-oxadiazole moieties were designed and synthesised. Most of the title compounds demonstrated potent telomerase inhibitory activity. SARs studies showed that the substitution of the methoxy group at $\mathbf{R^1}$ was very advantageous for telomerase activity, and the substitution of halogen for the *para* position of the phenyl ring at $\mathbf{R^2}$ significantly improved the telomerase inhibitory activity. However, replacing phenyl ring at $\mathbf{R^2}$ with aromatic fused rings, aromatic heterocycles and other substituents had also the significant effect on telomerase activity. In particular, compound **A33** substituted by styryl at $\mathbf{R^2}$ not only possessed strong activity against telomerase, but also exhibited moderately effective antiproliferative activity against all tested five human cancer cell lines, which was superior to telomerase inhibitor BIBR1532. Furthermore, it had no obvious toxicity towards human normal L-02 cell with IC_{50} of 2.21 mM. Flow cytometric analysis indicated that MGC-803 cell cycle was arrested in the G2/M phase by this compound, inducing MGC-803 cells apoptosis. Western blotting revealed that compound **A33** could significantly decrease the expression of dyskerin. In conclusion, it is believed that these results will help to regulate the expression of dyskerin protein through the rational design of small molecules in the future.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Supporting information

The following files are available free. ^{1}H NMR and ^{13}C NMR spectra and HRMS of all compounds. Fitting plot of compounds **A2**, **A5**, **A16**, **A20**, **A27**, **A33**, **B27** and **B33** for telomerase activity.

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