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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antiproliferative activity of aminoalkylated chalcones on three human cancer cells

Cui Li[1] · Gangqiang Wang[2] · Xueli Li[1] · Qiuan Wang[1]

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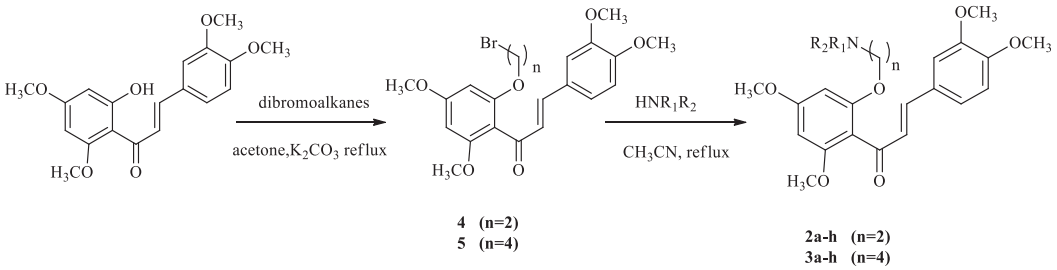
Abstract Two series of 16 novel aminoalkylated chalcone derivatives **2a–h** and **3a–h** were synthesized from 2′-hydroxy-3,4,4′,6′-tetramethoxychalcone (**1**) through extending alkoxy side chain at the 2′-position, and introducting amine hydrogen bond receptor at the end of the side chain. Their in vitro antiproliferative activities were evaluated on a panel of three human cell lines (Hela, HCC1954, and SK-OV-3) by CCK-8 assay. The results showed that all the target compounds, except compound **3e**, exhibited moderate to potent antiproliferative activities against these three human cancer cells with the IC_{50} values of 6.78–64.45 μmol/L, in particular compounds **2g** (on Hela cells), **2c** (on HCC1954 cells), and **2c**, **2d** (on SK-OV-3 cells) possess IC_{50} values below 10 μmol/L. It showed the introduction of aminoalkyl moiety at 2′-*O*-position of chalcone **1** resulted to produce the desired effect of increasing the antiproliferative activities, and the distance between the amino groups and chalcone moiety plays an important role, the optimal number of methylene units is two-carbon spacer.

Graphical abstract A series of 16 novel aminoalkylated chalcones were synthesized and their antiproliferative acivities on three human cancer cells were evaluated.



Keywords Chalcone · Aminoalkylated derivatives · Synthesis · Antiproliferative activity

Introduction

Chalcones are precursors in the biosynthesis of flavonoids and occur widely in medicinal plants. Chemically, they

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✉ Qiuan Wang
wangqa@hnu.edu.cn

[1] College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China

[2] School of Nuclear Technology and Chemistry & Biology, Hubei University of Science and Technology, Hubei 437100, China

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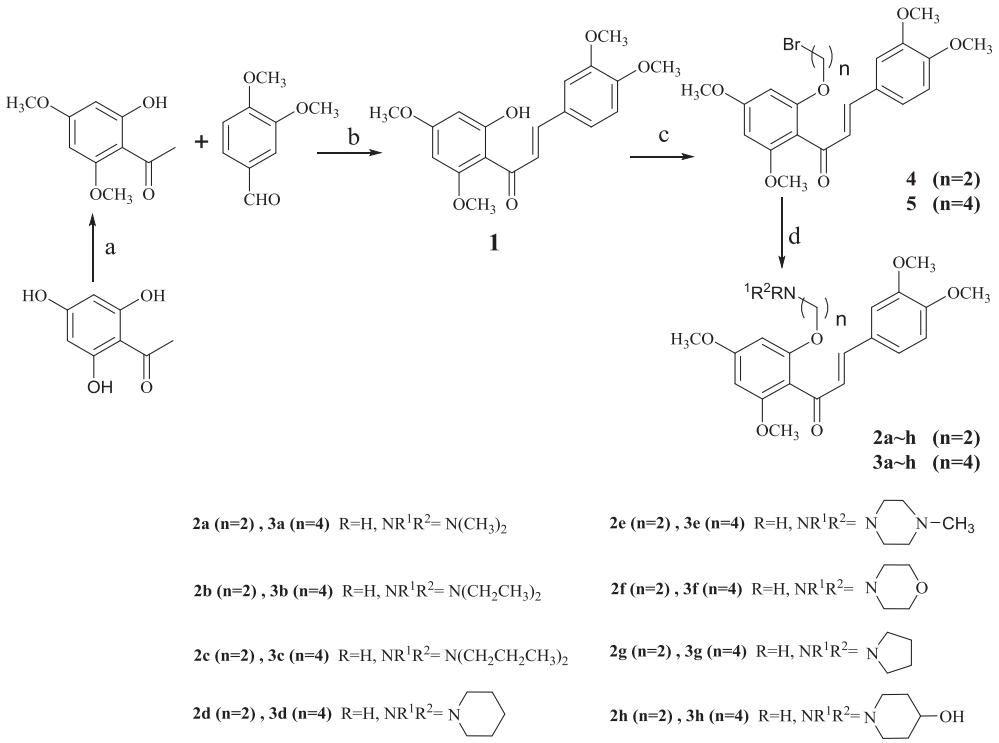
consist of two aromatic rings linked by a three-carbon α, β-unsaturated system. Chalcones have attracted much research attention because of their biological activity and pharmaceutical potential resulting from their antitumor, anti-inflammatory, antioxidant, and neuroprotective properties (Barbic et al. 2010; Campbell et al. 2016; Blanc et al. 2008; Abd-Rahman et al. 2014; Li et al. 2017). Among these properties, antitumor effects were most extensively examined (Kuppuswami et al. 2015; EI-Melige et al. 2017; Emami et al. 2016). However, the in vitro efficacy and mode of action of chalcones are controversial since polar polyphenols are poorly absorbed, do not conform to the Lipinski rules (Dominy et al. 2001; Lipinski 2004), and are rapidly metabolized by liver enzymes in plasma, leading to insignificant bioavailability (Abay et al. 2015). It thus remains a challenge to reconcile their poor bioavailability with putative health effects.

Most drugs contain nitrogen, and the introduction of the aminoalkyl group into molecules is a general strategy for improving bioactivity (Bandeira et al. 2016; Bao et al. 2008; Balakishan et al. 2010). Aminoalkylation of drugs could be used to increase the hydrophilic properties of drugs through the introduction of a polar function in their structure (Bonesi et al. 2008). The solubility in water of a drug could be further enhanced through the quaternization of the nitrogen atom in its aminoalkylated derivative and conversion into an ammonium salt. Little research has been reported on the synthesis and biological activity of chalcones with aminoalkyl moieties.

2′-Hydroxy-3,4,4′,6′-tetramethoxychalcone (**1**), a synthetic 2′-hydroxy polymethoxylated chalcone, posses an appealing pharmacological profile combining high antioxidant, and lipid peroxidation activity with potent soybean LOX inhibition (Detsi et al. 2009). On the basis of these results and following our previous work (Huang et al. 2014; Nguyen et al. 2017; Dong et al. 2015), herein we report the synthesis of two series of 16 novel aminoalkylated chalcone derivatives **2a–h** and **3a–h** from 2′-hydroxy-3,4,4′,6′-tetramethoxy chalcone (**1**) through extending alkoxy side chain at the 2′-position, and introducing amine hydrogen bond receptor at the end of the side chain. Their in vitro antiproliferative activities against three human cancer cell lines Hela (cervical carcinoma), HCC1954 (breast cancer), and SK-OV-3 (ovarian cancer) were evaluated using cell counting kit-8 (CCK-8) assay.

Results and discussion

Synthesis of novel aminoalkylated chalcone derivatives **2a–h** and **3a–h** from 2′-hydroxy-3,4,4′,6′-tetramethoxy chalcone (**1**) is shown in Scheme 1. Chalcone **1** was synthesized by aldol condensation of 2-hydroxy-4,6-dimethoxy acetophene with 3,4-dimethoxy benzaldeyde according to



Scheme 1 Sythesis of aminoalkylated polymethoxychalcone derivatives **2a–h** and **3a–h**. Reaction conditions: **a** $(CH_3)_2SO_4$, K_2CO_3, acetone, reflux; **b** 25% NaOH (aq), C_2H_5OH, r.t.; **c** K_2CO_3, dibromoalkanes, acetone, reflux; **d** amines, K_2CO_3, KI, CH_3CN, reflux

Table 1 Half-inhibitory concentrations (IC_{50} in μmol/L) of compounds **1**, **2a–h**, and **3a–h** on the human cancer cell lines

Compounds	Hela	HCC1954	SK-OV-3
1	>100	>100	>100
2a	10.03 ± 0.38	16.16 ± 0.72	11.16 ± 1.34
2b	10.44 ± 0.68	18.85 ± 2.42	12.01 ± 3.88
2c	12.29 ± 0.89	6.78 ± 0.43	8.15 ± 1.24
2d	13.43 ± 1.60	17.12 ± 0.58	8.87 ± 0.83
2e	11.62 ± 0.14	28.98 ± 3.01	16.87 ± 0.17
2f	22.24 ± 0.25	23.94 ± 0.49	19.94 ± 2.37
2g	8.80 ± 0.88	17.51 ± 2.25	14.33 ± 0.10
2h	12.7 ± 0.66	27.29 ± 4.12	19.16 ± 2.07
3a	29.45 ± 1.33	26.01 ± 0.94	45.18 ± 3.78
3b	40.83 ± 1.21	34.73 ± 0.57	48.44 ± 0.66
3c	33.45 ± 0.71	16.37 ± 0.70	58.52 ± 3.51
3d	37.06 ± 1.50	28.29 ± 2.37	49.63 ± 3.68
3e	>100	>100	>100
3f	46.58 ± 1.01	38.15 ± 1.42	40.10 ± 1.84
3g	38.63 ± 1.16	30.59 ± 3.81	64.45 ± 3.01
3h	51.79 ± 6.09	46.12 ± 1.87	54.18 ± 3.54
cis-Platin[a]	13.30 ± 1.93	29.32 ± 2.22	18.66 ± 0.46
Paclitaxel[a]	0.0055 ± 5.2E-07	0.009 ± 2.17E-06	0.0028 ± 3.36E-08
Staurosporin[a]	0.0112 ± 1.69E-06	0.037 ± 3E-06	0.0031 ± 3.13E-08

[a] *cis*-Platin Paclitaxel and Staurosporin were employed as positive controls

the reported procedure (Detsi et al. 2009; Fernandes et al. 2014). The coupling constant of 15.5–16.5 H_Z observed of ^{1}HNMR in olefinic protons Hα and Hβ indicates the formation of only the expected *E* isomer. Compounds **4** and **5** were the key intermediates, they were prepared from alkylation of 2′-OH group by using dihaloalkanes via Williamson ether synthesis (Dong et al. 2010). Thus, **1** was alkylated with the equivalent amount of potassium carbonate in acetone followed by the addition of excessive amounts of 1,2-dibromoethane or 1,4-dibromobutane furnished **4** or **5**. Subsequently, compounds **4** or **5** was reacted with two equivalent secondary amines, anhydrous K_2CO_3 and the catalytic amount of KI in CH_3CN at 60–65 °C. This process produced the desired target aminoalkylated chalcones **2a–h** and **3a–h** in moderate to good yields.

Chalcone **1** and 16 novel aminoalkylated chalcone derivatives **2a–h** and **3a–h** were investigated for their antiproliferative activity employing the CCK-8 assay with *cis*-Platin, Paclitaxel and Staurosporin as possitive controls against three human cancer cell lines (Hela, HCC1954, and SK-OV-3). Their activities were expressed by the concentration of drug inhibiting 50% cell growth (IC_{50}) and data are presented in Table 1. The dose-response curves for CCK-8 assay of compound **2g** on Hela cells, compound **2c** on HCC1954 cells, and compounds **2c**, **2d** on SK-OV-3 cells proliferation are shown in Fig. 1.

As show in Table 1, the parent chalcone **1** did not displayed any antiproliferative activity to the three cancer cells (IC_{50} > 100 μmol/L), while all aminoalkylated chalcone derivatives except **3e** showed moderate to potent anticancer activity to tested cell lines with IC_{50} values ranging from 6.78 to 64.45 μmol/L. Therefore, the comparision of these new synthesized aminoalkylated chalcones with parent chalcone revealed that the introduction of aminoalkyl moiety at 2′-*O*-position of chalcone **1** resulted to produce the desired effect of increasing the antiproliferative activities. It was established chalcones with an aminoalkyl moiety on the aromatic ring exhibit promising in vitro antiproliferative activity. This supports the hypothesis that nitrogen-containing chalcones would enhance biological activity compared to non-nitrogen analogs. A good number of synthesized derivatives showed remarkable more potency as compared to positive control *cis*-Platin, compounds **2a–h** series except **2f** were equal or more potent (lower IC_{50} values) against Hela cells with IC_{50} values of 8.80–13.43 μmol/L than the positive control *cis*-Platin (IC_{50} 13.30 μmol/L), compounds **2a–h**, **3a**, and **3c** were equal or more potent against HCC1954 cells with IC_{50} values of 6.78–28.98 μmol/L than the positive control *cis*-Platin (IC_{50} 29.32 μmol/L), and compounds **2a–h** series were equal or more potent against SK-OV-3 cells with IC_{50} values 8.15–19.16 μmol/L than the positive control *cis*-Platin (IC_{50} 18.66 μmol/L). In particular, compound **2g** characterized with pyrrolidinylethoxyl substituent on Hela cells, compound **2c** characterized with diethylaminoethoxyl substituent on HCC1954 cells, and compounds **2c**, **2d** characterized with piperidinylethoxyl substituent on SK-OV-3 cells showed markedly potency with IC_{50} value below 10 μmol/L. Furthermore, we have carried out some experiments to evaluate the synthesized derivatives' biological activitiy, unfortunately the biological of corresponding products showed higher IC_{50} values than Paclitaxel and Staurosporin.

With the increase of the length of alkyl chain of aminoalkylated chalcone from two-carbon to four-carbon spacer, there is a significant decrease in antiproferative activities against all the three cancer cells. It showed the distance between the amino groups and chalcone moiety plays an important role, the optimal number of methylene units is two-carbon spacer in our present experiments, and some aminoalkylated chalcone with two-carbon posses IC_{50} values of below 10 μmol/L.

Conclusion

In conclusion, two series of 16 novel aminoalkylated chalcone derivatives **2a–h** and **3a–h** were synthesized from 2′-hydroxy-3,4,4′,6′-tetramethoxychalcone (**1**). A good number of synthesized aminoalkylated chalcones exhibit comparable or higher antiproliferative activities than the positive control drug *cis*-Platin, some compounds (**2g** on

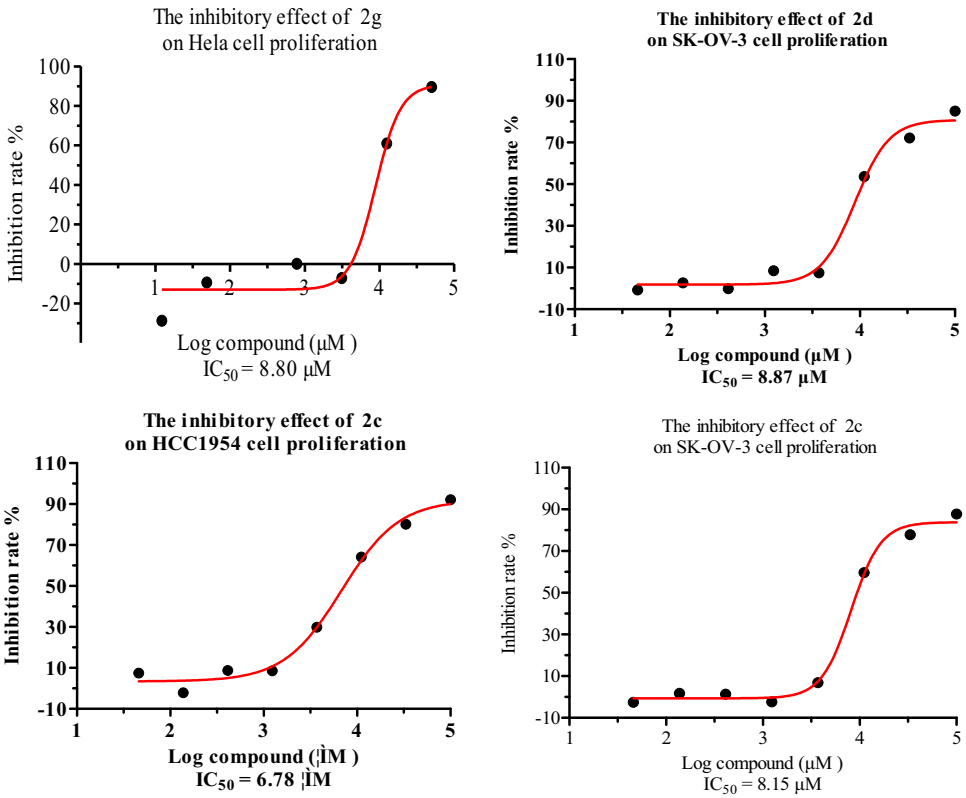


Fig. 1 The dose-response curves of compounds **2g** (on Hela), **2c** (on HCC1954), and **2c**, **2d** (on SK-OV-3) cell proliferation

Hela cells, **2c** on HCC1954 cells, and **2c**, **2d** on SK-OV-3 cells) possess IC_{50} values of below 10 μmol/L. It was established chalcones with an aminoalkyl moiety on the aromatic ring exhibit promising in vitro antiproliferative activity. This supports the hypothesis that nitrogen-containing chalcones would enhance biological activity compared to non-nitrogen analogs. The distance between the amino groups and chalcone moiety plays an important role, the optimal number of methylene units is two-carbon spacer. The aminoethylated chalcones are a class of potential antitumor agents and worthy of further investigation.

Experimental part

General

The ^{1}H NMR and ^{13}C NMR spectra were recorded using TMS as the internal standard in $CDCl_3$ with a Bruker-AV400 spectrometer at 400 and 100 MHz, respectively. The chemical shifts (δ) were measured by ppm, and coupling constant (J) was calculated in hertz (Hz). Mass spectra (MS), high-resolution mass spectrometry (HRMS) were determined with VG Autospec-3000 or Mat 95 XP spectrometer and Micromass ZQ 2000 mass spectrometer (Manchester, UK) by the EI or ESI method. Melting points were determined by an XRC-1 apparatus and were uncorrected. Column chromatography was carried out on silica gel 200–300 mesh (Qingdao Ocean Chemical Products of China). Commercially available AR or chemical pure reagents, and anhydrous solvent removed water and redistilled were employed.

2-Hydroxy-4,6-dimethoxyacetophenone and 2′-hydroxy-3,4,4′,6′-tetramethoxy chalcone (**1**) were prepared from phloroglucinol according to previous methods (Detsi et al. 2009; Chen et al. 2016).

*Synthesis of 2′-(2-bromoethoxy)-3,4,4′,6′-tetramethoxy chalcone (**4**) and 2′-(2-bromobutoxy)-3,4,4′,6′-tetramethoxy chalcone (**5**)*

1,2-Dibromoehtane or 1,4-dibromobutane (0.18 mL, 2 mmol) was added dropwise to a solution of 2′-hydroxy-3,4,4′,6′-tetramethoxy chalcone (0.5 g, 1.45 mmol) and potassium carbonate in dry acetone (50 mL), and the mixture (stirred at ambient temperature beforehand for 1 h) was refluxed for 24 h. The progress of the reaction was monitored by TLC. After cooling to room temperature, the mixture was filtered, the solvent was evaporated, and the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 3:1, volume ratio) to afford compound **4** or **5**.

2′-(2-Bromoethoxy)-3,4,4′,6′-tetramethoxychalcone (**4**) Yield: 87%, yellow oil. ^{1}H NMR (400 MHz, CDCl3): 7.21 (d, $J = 15.6$ Hz, 1H, β-H), 7.03–7.01 (m, 2H, α-H and 2-H), 6.83–6.77 (m, 2H, 5-H and 6-H), 6.13 (s, 1H, 5′-H), 6.07 (s, 1H, 3′-H), 4.19 (t, $J = 6.1$ Hz, 2H, OCH_2), 3.84 (s, 3H, 3-OCH_3), 3.82 (s, 3H, 4-OCH_3), 3.78 (s, 3H, 4′-OCH_3), 3.70 (s, 3H, 6′-OCH_3), 3.45 (t, $J = 6.0$ Hz, 2H, CH_2Br). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.12, 161.42, 158.08, 156.25, 150.35, 148.33, 143.96, 127.09, 126.34, 122.28, 111.86, 110.17, 109.15, 91.21, 90.91, 68.04, 55.21, 55.16, 55.10, 54.79, 27.96. MS(EI): *m/z* 450.07 $[M]^+$, HRMS(EI): *m/z* 450.0680 $[M]^+$ (calcd for $C_{21}H_{23}O_6Br$ 450.0678).

2′-(4-Bromobutoxy)-3,4,4′,6′-tetramethoxychalcone (**5**) Yield: 89%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, $J = 15.6$ Hz, 1H, β-H), 7.01–6.98 (m, 2H, α-H and 2-H), 6.81–6.72 (m, 2H, 5-H and 6-H), 6.09 (s, 1H, 5′-H), 6.06 (s, 1H, 3′-H), 3.89 (t, $J = 5.6$ Hz, 2H, OCH_2), 3.82 (s, 6H, 3,4-OCH_3), 3.77 (s, 3H, 4′-OCH_3), 3.6 9 (s, 3H, 6′-OCH_3), 3.23 (t, $J = 6.3$ Hz, 2H, CH_2Br), 1.90–1.70 (m, 4H, $2CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.33, 162.27, 158.77, 157.92, 151.19, 149.21, 144.58, 127.88, 127.30, 122.91, 112.16, 111.07, 109.96, 91.53, 91.03, 77.38, 77.07, 76.75, 67.55, 56.12–55.82, 55.48, 33.51, 29.19, 27.54. MS(EI): *m/z* 478.10 $[M]^+$, HRMS(EI): *m/z* 478.0997 $[M]^+$ (calcd for $C_{23}H_{27}O_6Br$ 478.0991).

*General procedure for the synthesis of aminoalkylated chalcone derivatives **2a–h** and **3a–h***

To a suspension of compound **4** or **5** (0.32 mmol) and anhydrous K_2CO_3 (0.64 mmol) in CH_3CN (5 mL), the corresponding secondary amine (0.32 mmol) and a catalytic amount of KI were added, and the resulting mixture was refluxed for 1 h. After filtering, the resulting filtrate was evaporated to dryness under reduced pressure. The residue was suspended in water (20.0 mL), and extracted with dichloromathane (3×25 mL). The combined organic were evaporated under reduced pressure. The residue was purified on a silica gel chromatography (petroleum ether/ethyl acetate = 3:1–1:1 with several drops of triethylamine, volume ratio) to afford **2a–h** or **3a–h**.

2′-(2-Dimethylaminoethoxy)-3,4,4′,6′-tetramethoxychalcone (**2a**) Yield: 81%, pale yellow oil. ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.17 (d, $J = 15.9$ Hz, 1H, β-H), 6.99 (d, $J = 16.0$ Hz, 1H, α-H), 6.97 (s, 1H, 2-H), 6.77 (d, $J = 2.6$ Hz, 1H, 5-H), 6.74 (d, $J = 5.0$ Hz, 1H, 6-H), 6.08 (s, 2H, 3′-H and 5′-H), 3.97 (t, $J = 5.8$ Hz, 2H, OCH_2), 3.80 (s, 6H, 3, 4-OCH_3), 3.75 (s, 3H, 4′-OCH_3), 3.67 (s, 3H, 6′-OCH_3), 2.55 (t, $J = 5.8$ Hz, 2H, CH_2N), 2.13 (s, 6H, $N(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.28, 161.23, 157.70, 156.88, 150.10, 148.12, 143.50, 126.88, 126.24, 121.87, 111.19, 110.03, 108.95, 90.64, 90.08, 66.55, 56.81, 54.93, 54.89, 54.86, 54.43, 44.95. MS(EI): *m/z* 415.20 $[M]^+$, HRMS(EI): *m/z* 415.2005 $[M]^+$ (calcd for $C_{23}H_{29}O_6N$ 415.1995).

2′-(2-Diethylaminoethoxy)-3,4,4′,6′-tetramethoxychalcone (**2b**) Yield: 75%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, $J = 16.1$ Hz, 1H, β-H), 7.01 (d, $J = 16.3$ Hz, 1H, α-H), 6.98 (s, 1H, 2-H), 6.78 (d, $J = 5.9$ Hz, 1H, 5-H), 6.75 (d, $J = 6.2$ Hz, 1H, 6-H), 6.10 (s, 2H, 3′-H and 5′-H), 4.02 (t, $J = 5.8$ Hz, 2H, OCH_2), 3.83 (s, 3H, 3-OCH_3), 3.82 (s, 3H, 4-OCH_3), 3.77 (s, 3H, 4′-OCH_3), 3.68 (s, 3H, 6′-OCH_3), 2.79 (t, $J = 5.7$ Hz, 2H, CH_2N), 2.54 (q, $J = 7.1$ Hz, 4H, $2NCH_2$), 0.91 (t, $J = 7.1$ Hz, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.52, 161.25, 157.66, 156.70, 150.19, 148.18, 143.77, 126.85, 126.22, 121.91, 110.98, 110.05, 109.00, 90.43, 90.22, 66.04, 54.96, 54.92, 54.89, 54.48, 50.09, 46.40, 10.13. MS(EI): *m/z* 443.21 $[M]^+$, HRMS(EI): *m/z* 443.2303 $[M]^+$ (calcd for $C_{25}H_{33}O_6N$ 443.2308).

2′-(2-Dipropylaminoethoxy)-3,4,4′,6′-tetramethoxychalcone (**2c**) Yield: 63%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, $J = 16.2$ Hz, 1H, β-H), 7.00 (d, $J = 16.1$ Hz, 1H, α-H), 6.97 (s, 1H, 2-H), 6.77 (s, 1H, 5-H), 6.74 (d, $J = 9.5$ Hz, 1H, 6-H), 6.08 (d, $J = 4.3$ Hz, 2H, 3′-H and 5′-H), 3.92 (t, $J = 6.3$ Hz, 2H, OCH_2), 3.81 (s, 6H, 3, 4-OCH_3), 3.76 (s, 3H, 4′-OCH_3), 3.67 (s, 3H, 6′-OCH_3), 2.67 (t, $J = 6.3$ Hz, 2H, CH_2N), 2.33–2.25 (m, 4H, $2NCH_2$), 1.29 (d, $J = 14.8$, 7.4 Hz, 4H, $2CH_2$), 0.71 (t, $J = 7.3$ Hz, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.26, 161.21, 157.68, 157.07, 150.10, 148.15, 143.39, 126.95, 126.29, 121.86, 111.12, 110.05, 108.97, 90.54, 89.97, 66.66, 55.87, 54.92, 54.88, 54.84, 54.41, 51.81, 51.68, 19.42, 10.77. MS(EI): *m/z* 471.23 $[M]^+$, HRMS(EI): *m/z* 471.2619 $[M]^+$ (calcd for $C_{27}H_{37}O_6N$ 471.2621).

2′-(2-Piperidinylethoxy)-3,4,4′,6′-tetramethoxychalcone (**2d**) Yield: 70%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, $J = 15.8$ Hz, 1H, β-H), 7.01 (d, $J = 15.9$ Hz, 1H, α-H), 6.97 (s, 1H, 2-H), 6.76 (m, 1H, 5-H, 6-H), 6.09 (d, $J = 5.1$ Hz, 2H, 3′-H, 5′-H), 4.11 (t, $J = 5.0$ Hz, 2H, OCH_2), 3.82 (s, 6H, 3, 4-OCH_3), 3.76 (s, 3H, 4′-OCH_3), 3.68 (s, 3H, 6′-OCH_3), 2.81 (t, $J = 5.0$ Hz, 2H, CH_2N), 2.52 (s, 4H, $2NCH_2$), 1.45 (m, 4H, $2CH_2$), 1.28 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.59, 161.30, 157.64, 156.32, 150.25, 148.20, 143.97, 126.73, 126.17, 121.93, 110.86, 110.07, 109.01, 90.38, 90.34, 64.93, 55.63, 54.97, 54.91, 54.51, 53.17, 23.56, 22.23. MS(EI): *m/z* 455.20 $[M]^+$, HRMS(EI): *m/z* 455.2305 $[M]^+$ (calcd for $C_{26}H_{33}O_6N$ 455.2308).

2′-[2-(1-Methylhexahydropyrazinyl)ethoxy]-3,4,4′,6′-tetramethoxychalcone (**2e**) Yield: 68%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, $J = 15.7$ Hz, 1H, β-H), 7.00 (d, $J = 15.8$ Hz, 1H, α-H), 6.97 (s, 1H, 2-H), 6.77 (d, $J = 5.8$ Hz, 1H, 5-H), 6.74 (d, $J = 7.6$ Hz, 1H, 6-H), 6.08 (d, $J = 5.5$ Hz, 2H, 3′-H, 5′-H), 4.00 (t, $J = 5.6$ Hz, 2H, OCH_2), 3.82 (s, 6H, 3, 4-OCH_3), 3.76 (s, 3H, 4′-OCH_3), 3.68 (s, 3H, 6′-OCH_3), 2.62 (t, $J = 5.6$ Hz, 2H, CH_2N), 2.42 (s, 4H, $2NCH_2$), 2.20 (s, 4H, $2CH_2$), 2.09 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.50, 161.19, 157.65, 156.75, 150.16, 148.17, 143.72, 126.83, 126.22, 121.89, 111.05, 110.02, 108.96, 90.49, 90.04, 66.30, 55.77, 54.96, 54.90, 54.88, 54.44, 53.90, 52.58, 44.87, 28.66, 13.18. MS(EI): *m/z* 470.21 $[M]^+$, HRMS(EI): *m/z* 470.2416 $[M]^+$ (calcd for $C_{25}H_{34}O_6N_2$ 470.2417).

2′-(2-Morpholinylethoxy)-3,4,4′,6′-tetramethoxychalcone (**2f**) Yield: 90%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, $J = 16.0$ Hz, 1H, β-H), 7.00 (d, $J = 16.1$ Hz, 1H, α-H), 6.97 (s, 1H, 2-H), 6.77 (d, $J = 5.7$ Hz, 1H, 5-H), 6.74 (d, $J = 7.5$ Hz, 1H, 6-H), 6.10 (s, 1H, 3′-H), 6.08 (s, 1H, 5′-H), 4.02 (t, $J = 5.4$ Hz, 2H, OCH_2), 3.82 (s, 6H, 3, 4-OCH_3), 3.77 (s, 3H, 4′-OCH_3), 3.68 (s, 3H, 6′-OCH_3), 3.50–3.44 (m, 4H, $2OCH_2$), 2.62 (t, $J = 5.3$ Hz, 2H, CH_2N), 2.42–2.36 (m, 4H, $2NCH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.54, 161.21, 157.66, 156.64, 150.24, 148.21, 143.85, 126.70, 126.18, 121.85, 111.03, 110.03, 108.91, 90.54, 90.07, 66.35, 65.74, 56.28, 54.95, 54.91, 54.89, 54.46, 53.13, 28.67, 13.18. MS(EI): *m/z* 457.21 $[M]^+$, HRMS(EI): *m/z* 457.2107 $[M]^+$ (calcd for $C_{25}H_{31}O_7N$ 457.2101).

2′-(2-Pyrrolidinylethoxy)-3,4,4′,6′-tetramethoxychalcone (**2g**) Yield: 75%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, $J = 16.0$ Hz, 1H, β-H), 7.00 (d, $J = 15.9$ Hz, 1H, α-H), 6.98 (s, 1H, 2-H), 6.78 (s, 1H, 5-H), 6.75 (d, $J = 7.8$ Hz, 1H, 6-H), 6.09 (s, 2H, 3′-H, 5′-H), 4.02 (t, $J = 5.8$ Hz, 2H, OCH_2), 3.82 (s, 6H, 3, 4-OCH_3), 3.76 (s, 3H, 4′-OCH_3), 3.68 (s, 3H, 6′-OCH_3), 2.73 (t, $J = 5.8$ Hz, 2H, CH_2N), 2.44 (s, 4H, $2CH_2$), 1.57 (dd, $J = 6.4$, 3.1 Hz, 4H, $2CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.52, 162.21, 158.67, 157.86, 151.11, 149.13, 144.68, 127.88, 127.27, 122.89, 112.07, 111.00, 109.94, 91.47, 91.05, 68.26, 55.95, 55.91, 55.87, 55.45, 54.80, 54.49, 23.41. MS(EI): *m/z* 441.20$[M]^+$, HRMS(EI): *m/z* 441.2159 $[M]^+$ (calcd for $C_{25}H_{31}O_6N$ 441.2151).

2′-[2-(4-Hydroxypiperidinyl)ethoxy]-3,4,4′,6′-tetramethoxychalcone (**2h**) Yield: 85%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, $J = 15.9$ Hz, 1H, β-H), 7.00 (d, $J = 16.0$ Hz, 1H, α-H), 6.98 (s, 1H, 2-H), 6.78 (s, 1H, 5-H), 6.75 (d, $J = 6.4$ Hz, 1H, 6-H), 6.08 (d, $J = 2.7$ Hz, 2H, 3′-H, 5′-H), 4.01 (t, $J = 5.7$ Hz, 2H, OCH_2), 3.82 (s, 6H, 3, 4-OCH_3), 3.76 (s, 3H, 4′-OCH_3), 3.68 (s, 3H, 6′-OCH_3), 3.50 (m, 1H, OH), 2.74–2.66 (m, 2H, CH_2N), 2.64 (t, $J = 5.6$ Hz, 2H, CH_2), 2.13 (t, $J = 6.6$ Hz, 2H, CH_2), 1.96 (s, 1H, OH), 1.75–1.63 (m, 2H, CH_2), 1.45–1.32 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.66, 161.26, 157.67, 156.70, 150.22, 148.17, 143.87, 126.80, 126.18, 121.94, 110.97, 110.09, 109.05, 90.53, 90.12, 66.06, 55.64, 54.97, 54.92, 54.91, 54.48, 50.45, 33.10. MS(EI): *m/z* 471.22 $[M]^+$, HRMS(EI): *m/z* 471.2230 $[M]^+$ (calcd for $C_{26}H_{33}O_6N$ 471.2257).

2′-(4-Dimethylaminobutoxy)-3,4,4′,6′-tetramethoxychalcone (**3a**) Yield: 80%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, $J = 15.6$ Hz, 1H, β-H), 7.00–6.97 (m, 2H, α-H, 2-H), 6.77 (d, $J = 2.7$ Hz, 1H, 5-H), 6.74 (d, $J = 4.6$ Hz, 1H, 6-H), 6.06 (s, 2H, 3′-H, 5′-H), 3.86 (t, $J = 6.1$ Hz, 2H, OCH_2), 3.80 (s, 6H, 3, 4-OCH_3), 3.74 (s, 3H, 6′-OCH_3), 3.66 (s, 3H, 4′-OCH_3), 2.11–2.06 (m, 2H, NCH_2), 2.00 (s, 6H, $2CH_3$), 1.68–1.53 (m, 2H, CH_2), 1.47–1.36 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.35, 162.23, 158.75, 158.17, 151.12, 149.20, 144.38, 128.00, 127.32, 122.89, 111.05, 109.98, 91.54, 90.90, 77.35, 77.04, 76.72, 68.52, 59.07, 56.07–55.79, 55.44, 46.06, 45.10, 26.94, 23.93, 11.18. MS(ESI): *m/z* 444.10 $[M+H]^+$, HRMS(EI): *m/z* 443.2302 $[M]^+$ (calcd for $C_{25}H_{33}O_6N$ 443.2308).

2′-(4-Diethylaminobutoxy)-3,4,4′,6′-tetramethoxychalcone (**3b**) Yield: 82%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, $J = 16.0$ Hz, 1H, β-H), 7.09–7.06 (m, 2H, α-H, 2-H), 6.86 (d, $J = 4.0$ Hz, 1H, 5-H), 6.83 (d, $J = 3.6$ Hz, 1H, 6-H), 6.16 (s, 2H, 3′-H, 5′-H), 3.96 (t, $J = 6.2$ Hz, 2H, OCH_2), 3.90 (s, 6H, 3, 4-OCH_3), 3.84 (s, 3H, 6′-OCH_3), 3.76 (s, 3H, 4′-OCH_3), 2.40 (d, J = 7.1 Hz, 2H, NCH_2), 2.39–2.31 (m, 4H, $2NCH_2$), 1.69–1.66 (m, 2H, CH_2), 1.49–1.46 (m, 2H, CH_2), 0.94–0.90 (m, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.32, 162.20, 158.69, 158.16, 151.07, 149.14, 144.34, 127.94, 127.26, 122.88, 112.09, 111.01, 109.87, 91.49, 90.78, 68.61, 56.03–55.74, 55.41, 52.34, 46.55, 27.22, 23.21, 11.55. MS(ESI): *m/z* 472.30 $[M+H]^+$, HRMS(EI): *m/z* 471.2627 $[M]^+$ (calcd for $C_{27}H_{37}O_6N$ 471.2621).

2′-(4-Dipropylaminobutoxy)-3,4,4′,6′-tetramethoxychalcone (**3c**) Yield: 78%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, $J = 16.1$ Hz, 1H, β-H), 7.01–6.98 (m, 2H, α-H, 2-H), 6.78 (d, $J = 4.5$ Hz, 1H, 5-H), 6.75 (d, $J = 2.8$ Hz, 1H, 6-H), 6.07 (s, 2H, 3′-H, 5′-H), 3.86 (t, $J = 6.2$ Hz, 2H, OCH_2), 3.81 (s, 6H, 3, 4-OCH_3), 3.76 (s, 3H, 6′-OCH_3), 3.68 (s, 3H, 4′-OCH_3), 2.26 (t, $J = 7.3$ Hz, 2H, NCH_2), 2.15–2.19 (m, 4H, $2NCH_2$), 1.61–1.56 (m, 2H, CH_2), 1.40–1.37 (m, 2H, CH_2), 1.30–1.25 (m, 4H, $2CH_2$), 0.72 (t, $J = 7.3$ Hz, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.26, 162.21, 158.71, 158.21, 151.06, 149.14,

144.28, 127.96, 127.28, 122.86, 112.14, 111.01, 109.88, 91.51, 90.79, 68.69, 56.0–55.72, 55.40, 53.54, 27.13, 23.30, 20.04, 11.89. MS(ESI): *m/z* 500.20 $[M+H]^+$, HRMS (EI): *m/z* 499.2870 $[M]^+$ (calcd for $C_{29}H_{41}O_6N$ 499.2934).

2′-(4-Piperidinylbutoxy)-3,4,4′,6′-tetramethoxychalcone (**3d**) Yield: 74%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, $J = 15.9$ Hz, 1H, β-H), 7.10–7.07 (m, 2H, α-H, 2-H), 6.87 (s, 1H, 5-H), 6.84 (d, $J = 6.1$ Hz, 1H, 6-H), 6.16 (d, $J = 5.6$ Hz, 2H, 3′-H, 5′-H), 3.96 (t, $J = 6.0$ Hz, 2H, OCH_2), 3.91 (s, 6H, 3, 4-OCH_3), 3.86 (s, 3H, 6′-OCH_3), 3.77 (s, 3H, 4′-OCH_3), 2.28 (s, 2H, NCH_2), 2.25 (d, $J = 7.9$ Hz, 4H, $2NCH_2$), 1.70–1.67 (m, 2H, CH_2), 1.57–1.49 (m, 6H, $3CH_2$), 1.37 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.22, 158.72, 158.13, 151.11, 149.18, 144.52, 127.95, 127.29, 122.93, 111.02, 109.88, 91.44, 90.82, 68.56, 58.83, 56.07–55.79, 55.45, 54.28, 27.24, 25.71, 24.28, 23.21. MS (EI): *m/z* 484.27 $[M+H]^+$, HRMS(EI): *m/z* 483.2615 $[M]^+$ (calcd for $C_{28}H_{37}O_6N$ 483.2621).

2′-[4-(1-Methylhexahydropyrazinyl)butoxy]-3,4,4′,6′-tetramethoxychalcone (**3e**) Yield: 65%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, $J = 16.0$ Hz, 1H, β-H), 7.03–6.94 (m, 2H, α-H, 2-H), 6.78 (s, 1H, 5-H), 6.75 (d, $J = 6.2$ Hz, 1H, 6-H), 6.06 (d, $J = 4.1$ Hz, 2H, 3′, 5′-H), 3.87 (t, $J = 5.9$ Hz, 2H, OCH_2), 3.81 (s, 6H, 3, 4-OCH_3), 3.76 (s, 3H, 6′-OCH_3), 3.67 (s, 3H, 4′-OCH_3), 2.39–2.12 (m, 13H, $5NCH_2$, NCH_3), 1.65–1.55 (m, 2H, CH_2), 1.50–1.38 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.34, 162.17, 158.64, 158.05, 151.04, 149.10, 144.38, 127.83, 127.18, 122.88, 111.92, 110.97, 109.74, 91.35, 90.69, 68.41, 57.96, 55.99–55.73, 55.39, 54.92, 52.87, 45.91, 27.06, 23.33. MS (EI): *m/z* 498.28 $[M]^+$, HRMS(EI): *m/z* 498.2724 $[M]^+$ (calcd for $C_{28}H_{38}O_6N_2$ 498.2730).

2′-(4-Morpholinylbutoxy)-3,4,4′,6′-tetramethoxychalcone (**3f**) Yield: 92%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, $J = 15.9$ Hz, 1H, β-H), 7.11–7.05 (m, 2H, α-H, 2-H), 6.86 (s, 1H, 5-H), 6.83 (d, $J = 8.5$ Hz, 1H, 6-H), 6.15 (d, $J = 6.6$ Hz, 2H, 3′-H, 5′-H), 3.96 (t, $J = 5.9$ Hz, 2H, OCH_2), 3.91 (s, 3H, 3-OCH_3), 3.90(s, 3H, 4-OCH_3), 3.85 (s, 3H, 6′-OCH_3), 3.77 (s, 3H, 4′-OCH_3), 3.66–3.57 (m, 4H, $2OCH_2$), 2.40–2.24 (m, 6H, $3NCH_2$), 1.83–1.65 (m, 2H, CH_2), 1.63–1.50 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.47, 162.23, 158.65, 157.93, 151.15, 149.16, 144.55, 127.76, 127.16, 122.90, 111.88, 111.01, 109.82, 91.39, 90.78, 68.23, 66.08, 65.03, 57.95, 55.91, 55.43, 52.79, 44.87, 43.65, 26.85, 22.26. MS(EI): *m/z* 485.23 $[M]^+$, HRMS(EI): *m/z* 485.2408 $[M]^+$ (calcd for $C_{27}H_{35}O_7N$ 485.2414).

2′-(4-Pyrrolidinylbutoxy)-3,4,4′,6′-tetramethoxychalcone (**3g**) Yield: 75%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, $J = 15.9$ Hz, 1H, β-H), 7.09 (d, $J = 12.2$ Hz, 2H, α-H, 2-H), 6.89–6.82 (m, 2H, 5-H, 6-H), 6.16 (d, $J = 5.6$ Hz, 2H, 3′-H, 5′-H), 3.96 (t, $J = 6.0$ Hz, 2H, OCH_2), 3.91 (s, 6H, 3-OCH_3, 4-OCH_3), 3.86 (s, 3H, 6′-OCH_3), 3.77 (s, 3H, 4′-OCH_3), 2.28 (s, 2H, NCH_2), 2.25 (d, $J = 7.9$ Hz, 4H, $2NCH_2$), 1.76–1.61 (m, 2H, CH_2), 1.56 (d, $J = 7.1$ Hz, 2H, CH_2), 1.52–1.41 (m, 4H, $2CH_2$), 1.37 (d, $J = 4.8$ Hz, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.32, 162.19, 158.56, 157.89, 151.10, 149.12, 144.42, 127.74, 127.13, 122.86, 111.85, 111.02, 109.86, 91.32, 90.79, 68.26, 55.84, 55.36, 53.32, 26.86, 24.58, 23.61, 23.20. MS(ESI): *m/z* 470.30 $[M+H]^+$, HRMS(EI): *m/z* 469.2459 $[M]^+$ (calcd for $C_{27}H_{35}O_6N$ 469.2464).

2′-[4-(4-Hydroxypiperidinyl)butoxy]-3,4,4′,6′-tetramethoxychalcone (**3h**) Yield: 85%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, $J = 16.6$ Hz, 1H, β-H), 7.14–7.02 (m, 2H, α-H, 2-H), 6.87–6.82 (m, 2H, 5, 6-H), 6.16 (d, $J = 5.9$ Hz, 2H, 3′-H, 5′-H), 3.96 (t, $J = 5.6$ Hz, 2H, OCH_2), 3.89 (s, 6H, 3, 4-OCH_3), 3.85 (s, 3H, 6′-OCH_3), 3.77 (s, 3H, 4′-OCH_3), 3.66 (s, 1H, OCH), 2.78–2.67 (m, 2H, NCH_2), 2.43–2.32 (m, 2H, NCH_2), 2.22–2.05 (m, 2H, NCH_2), 1.74–1.52 (m, 6H,CH_2), 1.30–1.20 (m, 3H, CH_2, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.32, 162.19, 158.56, 157.89, 151.10, 149.12, 144.42, 127.74, 127.13, 122.86, 111.02, 109.86, 91.32, 90.79, 68.26, 55.84, 55.36, 53.36, 26.86, 24.58, 23.61, 23.20. MS(EI): *m/z* 499.25 $[M]^+$, HRMS(EI): *m/z* 499.2565 $[M]^+$ (calcd for $C_{28}H_{37}O_7N$ 499.2570).

In vitro assay for antiproliferative activity

Hela, HCC-1954, and SK-OV-3 cells were all cultured in a medium supplemented with 10% fetal bovine serum and 1% penicilin-streptomycin in a humidified atmosphere of 5% CO_2 at 37 °C, respectively, and Hela was maintained in RPMI-L640 medium. While HCC1954 and SK-OV-3 were maintained in DMEM/F12 medium. 20 mmol/L stock solution of the tested compounds including control were prepared with DMSO. The highest DMSO concentration of medium (0.5%) did not have significant effect on determined celluar functions.

Proliferative of Hela, HCC1954, and SK-OV-3 cells was evaluated by CCK-8 (Dojindo, Kumamoto, Japan) assay, according to the manufacture's instructions. This assay is based on the cleavage of the tetrazolium Salt WST-8 by mitochondrial dehydrogenase in viable cells (Chen et al. 2015). Briefly, 1×10^3 cells/well were incubated with 45 µL culture medium in 384-well plates. After being adhered to the well, the cells were treated with 5 µL of tested compounds at different concentrations, and then cultured for 72 h before addition of 5 µL CCK-8 to the culture medium in

each well. After 2–4 h incubation at 37 °C, absorbance at 450 nm of each well was measured with a fluorimeter (Novostar, BMG LABTECH, Germany). Each experiment was reported three times, and the data represented the mean of all measurements. The IC_{50} values were calculated using the Graphpad Prism 5 software.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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