European Journal of Medicinal Chemistry 54 (2012) 175–187

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and antitumor activity of formononetin nitrogen mustard derivatives

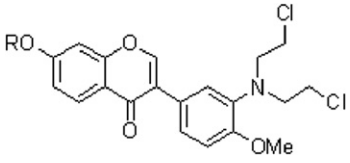
Jie Ren, Hua-Jin Xu, Hong Cheng, Wen-Qun Xin, Xin Chen*, Kun Hu*

School of Pharmaceutical Engineering & Life Science, Changzhou University, 1 Gehu Road, Changzhou, Jiangsu 213164, PR China

HIGHLIGHTS

- Sixteen novel formononetin nitrogen mustard derivatives were designed and synthesized.
- Their cytotoxic activities to human tumor *in vitro* have been screened.
- The pharmacological results showed that many of the new derivatives displayed more potent cytotoxicity than alkeran.
- Compounds **6d** and **6n** could induce cell cycle arrest at G2/M phase and cell apoptosis.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 22 November 2011
Received in revised form
21 March 2012
Accepted 27 April 2012
Available online 7 May 2012

Keywords:
Formononetin
Nitrogen mustard
Synthesis
Cytotoxicity
Cell cycle
Apoptosis

ABSTRACT

A series of formononetin nitrogen mustard derivatives were synthesized and evaluated *in vitro* for their cytotoxicity against five cancer cell lines (SH-SY5Y, HCT-116, DU-145, Hela and SGC-7901). The pharmacological results showed that many of the new derivatives displayed more potent cytotoxicity than alkeran. Furthermore, compounds **6d** and **6n** could induce cell cycle arrest at G2/M phase and cell apoptosis.

1. Introduction

Isoflavonoids are a broad class of polyphenolic secondary metabolites that are abundant in plants [1,2] and in various common foods, such as apples, onions, tea, and red wine [3,4]. Isoflavonoids have attracted considerable research interests for a long time because of their important biological and pharmacological properties. Formononetin **1**, one type of isoflavonoids, was reported to have many biological activities, including antioxidant, antidiabetic, antiestrogenic, antibacterial, antiangiogenic effects, and so on [5–9]. It is also a potent aryl hydrocarbon receptor agonist *in vitro* [9]. Xiang et al. [10] found that formononetin fatty acid esters had potential weight loss and hypolipidemic activities. The previous studies have showed that formononetin and its derivatives exhibited potent antiproliferative activities against two human tumor cells (Jurkat and HepG-2) *in vitro* [11].

DNA bifunctional alkylation agents containing nitrogen mustard moiety are an important class of anticancer drugs [12,13]. Nitrogen mustards, such as cyclophosphamide, chlorambucil and melphalan, are widely used as antitumor drugs. Nitrogen mustards are believed to exert their biological activity through interstrand cross-linking in the major groove of DNA, and this linkage represents the most toxic

* Corresponding authors. Tel./fax: +86 519 86334598.
E-mail addresses: xinchen@cczu.edu.cn (X. Chen), hukun1979@163.com (K. Hu).

0223-5234/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2012.04.039

of all alkylation events [14,15]. However, those nitrogen mustards are highly reactive agents, easily react with other cellular components such as proteins and genes, and result in loss of therapeutic activity of the drugs against malignancy, and produce many unwanted side-effects including bone marrow toxicity and genotoxicity [16,17]. Melphalan, also designed as alkeran, is a bifunctional alkylating agent. Its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells [18].

During the past several years, many nitrogen mustard structural modifications have been envisioned to increase their cytotoxicity, especially for their specificity toward tumor cells [19]. But to the best of our knowledge, there have been no literature reports regarding formononetin nitrogen mustard derivatives so far. In our present study, we have designed and synthesized a series of formononetin nitrogen mustard derivatives, and evaluated their anticancer activity against several cancer cell lines *in vitro* in search of new potent and selective anticancer agents, especially for estrogen-dependent cancer. We also elucidated the possible mechanism of cell growth inhibition by these new derivatives.

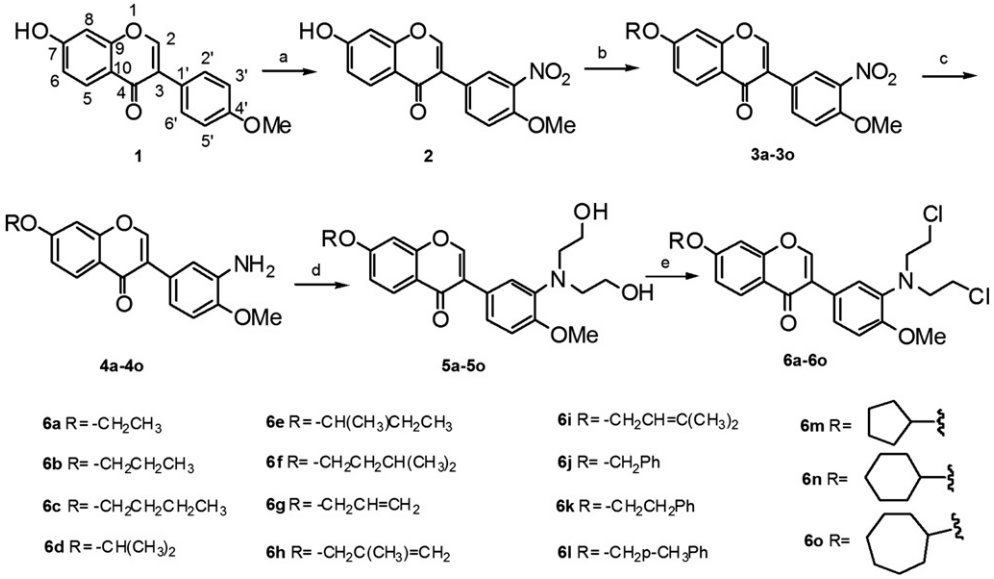
2. Chemistry

In order to investigate the structure–activity relationship of the formononetin N-mustard conjugates, we introduced several different alkyl groups to the 7-hydroxy in formononetin. The novel formononetin nitrogen mustard derivatives (**6a**–**6o**) were obtained through the synthetic route shown in Scheme 1. Firstly, the nitration of formononetin (**1**) at the 3′-position was carried out by reacting **1** with concentrated HNO_3 and concentrated H_2SO_4 in AcOH at 50 °C overnight, affording 3′-nitro formononetin (**2**) in 75% yield. In the second step, the 7-OH group in **2** was alkylated with various substituents by reacting **2** with the corresponding alkyl bromide in refluxing acetone and in the presence of K_2CO_3 (for compounds **3a**–**3l**), or by Mitsunobu reaction (for compounds **3m**–**3o**). The nitro group in compounds **3a**–**3o** was reduced by zinc powder in EtOH and AcOH, giving anilines **4a**–**4o**. And then **4a**–**4o** were reacted with ethylene oxide in AcOH to afford 3′-bis(2-hydroxyethyl)amino formononetin derivatives **5a**–**5o**. Finally, the target compounds **6a**–**6o** were obtained by refluxing compounds **5a**–**5o** with $SOCl_2$ in DCM. Free 7-OH formononetin N-mustard derivative **8** was obtained through the synthetic route shown in Scheme 2. Compound **5j** was subjected to debenzylation through hydrogenolysis in MeOH, giving intermediate **7**, and then the title compound **8** was obtained by treating **7** with $SOCl_2$ in DCM. The structures of all the final products **6a**–**6o** and **8** were confirmed by their IR, MS, ^1H NMR and ^{13}C NMR spectral properties.

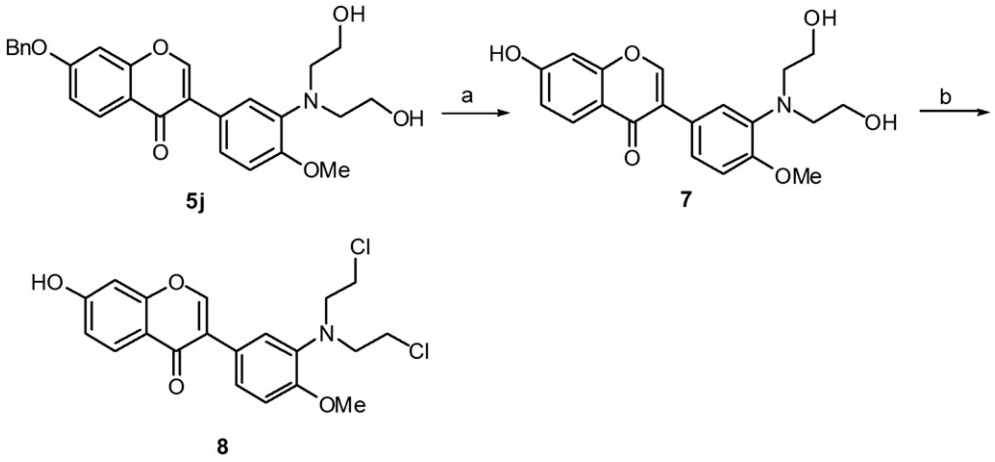
3. Results and discussion

3.1. In vitro cytotoxicity

The newly synthesized formononetin nitrogen mustard derivatives **6a**–**6o** and **8** were screened for *in vitro* cytotoxicity against five cancer cell lines, including SH-SY5Y (human neuroblastoma cell line), HCT-116 (human colon cancer cell line), DU-145 (human prostate carcinoma cell line), Hela (human cervical carcinoma cell line) and SGC-7901 (human gastric cell line), by the standard MTT assay, and using alkeran as a positive control. Antitumor potency of the compounds was indicated by IC_{50} values that were calculated by linear regression analysis of the concentration–response curves obtained for each compound, and the results are summarized in Table 1. As shown in Table 1, all the new compounds exhibited more potent inhibitory activity against HCT-116, SH-SY5Y and DU-145 than formononetin. For SGC-7901 and Hela cell lines, most of the new compounds shown weaker inhibitory activity than formononetin, but they were more potent than alkeran. Among the new derivatives, **6d** possessed significant cytotoxicity against HCT-116 with the IC_{50} value at 3.8 μM, **6f** and **6k** had stronger inhibitory activity against DU-145 with the IC_{50} values at 6.6 μM and 7.57 μM respectively, and **6n** with the IC_{50} value at 8.29 μM against Hela. Compared to alkeran, compounds **6d**, **6e**, **6k**, **6n**, **6o** and **8** possessed more potent inhibitory effects against SH-SY5Y with the IC_{50} values at 2.17 μM, 3.58 μM, 3.84 μM, 4.44 μM, 2.08 μM and 2.7 μM respectively, reflecting the selectivity for a particular human neuroblastoma cancer cell type.



Scheme 1. Synthesis of formononetin nitrogen mustard derivatives (**6a**–**6o**). Reagents and conditions: (a) concentrated HNO_3, concentrated H_2SO_4, AcOH, 50 °C, 12 h, 75%; (b) Method A: K_2CO_3, R–Br, acetone, reflux, 3–8 h, 79–87% (for **3a**–**3l**); Method B: DIAD, PPh_3, THF, R–OH, 0 °C to rt, overnight, 65–77% (for **3m**–**3o**); (c) Zn, EtOH, HOAc, reflux, 1–2 h, 78–85%; (d) ethylene oxide, HOAc, rt, overnight, 70–82%; (e) $SOCl_2$, DCM, reflux, 1.5 h, 66–75%.



Scheme 2. Synthesis of formononetin nitrogen mustard derivative **8**. Reagents and conditions: (a) H_2, 10% Pd/C, MeOH, rt, 1 h, 90%; (b) $SOCl_2$, DCM, reflux, 1.5 h, 70%.

From Table 1, the new derivatives with branched alkyl groups (**6d**, **6e**, **6f**), phenyl groups (**6j**, **6k**, **6l**), cycloalkyl groups (**6m**, **6n**, **6o**) and free hydroxyl group (**8**) at the 7-position were more cytotoxic toward HCT-116 cell growth *in vitro* than the derivatives with straight-chain alkyl (**6a**, **6b**, **6c**) and alkenyl groups (**6g**, **6h**, **6i**). In contrast, the branched alkyl – (**6d**, **6e**, **6f**), cycloalkyl – (**6m**, **6n**, **6o**) substituted compounds and unsubstituted **8** were more potent in inhibiting SH-SY5Y cell growth than those substituted by alkyl-phenyl (**6j**, **6k**, **6l**) and straight-chain alkyl (**6a**, **6b**, **6c**) groups. For DU-145 and Hela cell lines, cycloalkyl-substituted compounds (**6m**, **6n**, **6o**) possessed stronger inhibitory efforts than other derivatives. However, there were some exceptions, for example **6e** had the lowest cytotoxicity, **6a** and **6g** had relatively higher cytotoxicity against HCT-116 cell line, and **6k** had higher cytotoxicity against SH-SY5Y cell line. It is interesting to note that the derivatives with cycloalkyl groups (**6m**, **6n**, **6o**) had potent inhibitory efforts, and their activities seem to be related to the size of cycloalkyl groups, and the roughly inhibitory effects tendency was cyclopentyl (**6m**) < cyclohexyl (**6n**) < cycloheptyl (**6o**). These results indicated that the introduction of bulky groups at the 7-hydroxy position might facilitate the increase of the compounds' cytotoxic activities.

For against DU-145 cell line, the introduction of N-mustard to the 3′-position of formononetin had greatly enhanced the cytotoxicity of the derivatives compared to formononetin and alkeran. The most active compound was **6f** with the IC_{50} value at 6.6 μM, followed by **6k** (IC_{50} at 7.57 μM), **6c** (IC_{50} at 8.28 μM), whereas, derivatives **6a**, **6b**, **6e** and **6j** exhibited the weakest inhibitory activity. The data in Table 1 for DU-145 cell line also show that the compounds with cycloalkyl moieties (**6m**, **6n**, **6o**) had stronger cytotoxicity than other derivatives. However, compounds **6f**, **6k** and **6c**, which contained isopentyl, phenethyl and *n*-butyl groups, respectively, were exceptions; they exhibited extraordinary cytotoxicity against DU-145 cell line. In contrast, the free hydroxyl derivative **8** was more potent in inhibiting HCT-116, SH-SY5Y and SGC-7901 cells growth than estrogen-dependent cancer cell lines (DU-145 and Hela). This result indicated that the introduction of alkyl groups at 7-hydroxy position significantly facilitated to increase cytotoxic activities of the compounds against Hela cell line. However, for other four cancer cell lines, the introduction of an alkyl group at 7-hydroxy position didn't enhance the cytotoxicity of the derivatives.

Table 1
The cytotoxicity of formononetin nitrogen mustard derivatives.

Compd.	IC_{50} (μmol/L)				
	HCT-116	SH-SY5Y	DU-145	Hela	SGC-7901
6a	8.47	11.92	23.88	10.73	12.97
6b	15.23	7.89	28.84	12.76	>100
6c	17.05	16.28	8.28	11.8	11.78
6d	3.8	2.17	19.53	12.48	9.21
6e	20.17	3.58	28.84	18.85	47.51
6f	7.67	10.41	6.6	9.81	9.47
6g	7.54	4.51	15.42	9.22	10.21
6h	14.59	10.83	15.6	18.32	15.42
6i	13.79	5.25	12.15	18.02	19.79
6j	4.97	11.41	26.48	16.37	18.81
6k	8.05	3.84	7.57	17.79	11.04
6l	9.41	49.93	18.76	12.63	7.73
6m	8.75	5.13	11.06	19.31	15.22
6n	6.54	4.44	11.18	8.29	15.76
6o	5.72	2.08	10.09	8.85	14.26
8	4.1	2.7	22.57	56.26	8.2
Formononetin	60.97	>100	>100	8.51	2.17
Alkeran	20.9	5.5	96.31	23.99	50.96

3.2. Effect of compounds *6d* and *6n* on cell cycle arrest in HCT-116 and Hela cells

It was reported that DNA damage induced by DNA alkylating agents is known to cause cell cycle delay and arrest the cell cycle progression predominantly at the G2/M boundary [20]. Therefore, we chose two of our most active compounds **6d** and **6n** for investigating their effects on the distribution of cells in the cell cycle. To assess whether cell growth inhibition induced by the two compounds is mediated via alternations in cell cycle progression, DNA cell cycle analysis was performed. As shown in Fig. 1, compared with the control, compounds **6d** and **6n** treatment resulted in a dose-dependent accumulation of cells in the G2/M phase accompanied by a decrease in S phase (Fig. 1A). The percentage of cells in the G2/M fraction increased 24.84% and 21.33%-fold when treated with 8 μM of compound **6d** and 15 μM of compound **6n**, respectively, compared to a vehicle control. The results indicated that compounds **6d** and **6n** could induce G2/M cell cycle arrest.

3.3. Effect of compounds *6d* and *6n* on cell apoptosis in HCT-116 and Hela cells

In order to evaluate whether tested compounds-mediated inhibition in cell growth is due to the induction of apoptosis, Annexin-V/PI staining was used to detect the apoptotic ratio of

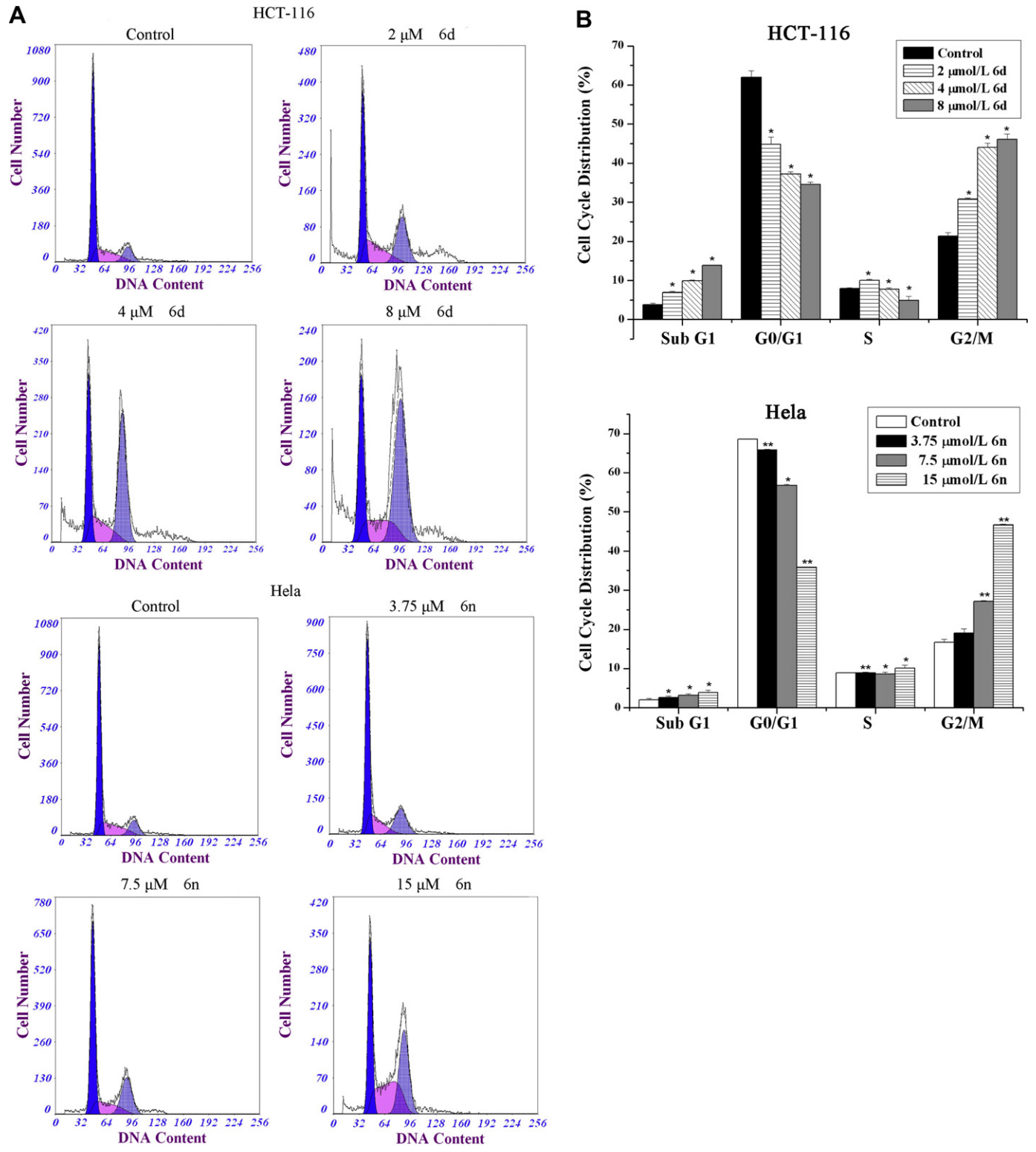


Fig. 1. Effects of compounds **6d** and **6n** on cell cycle of HCT-116 and Hela cells. Cells were treated with compounds **6d** (2, 4, 8 μM) and **6n** (3.75, 7.5, 15 μM) for 48 h, and the DNA content of 10,000 events was analyzed by flow cytometry. The profiles showed the cell cycle (A) and the proportions (%) in each phase (B) of HCT-116 and Hela cells treated with compounds **6d** and **6n**, respectively.

compounds **6d** and **6n**-treated cells. As shown in Fig. 2, after treatment with 8 μM of **6d** in HCT-116 cells and 10 μM of **6n** in Hela cells for 48 h, the early- to mid-apoptotic cells (right lower section of fluorocytogram) represented 38.1% and 8.83% of the total cells, respectively, whereas the control had only 1.62% and 2.93% apoptotic cells. Meanwhile, the late apoptotic and necrotic cells (right upper section of fluorocytogram) represented 43.72% and 30.1% of the total cells, whereas the control had only 0.43% and 1.98% necrotic cells, respectively. The result confirmed the induction of apoptosis upon treatment with compounds **6d** and **6n**.

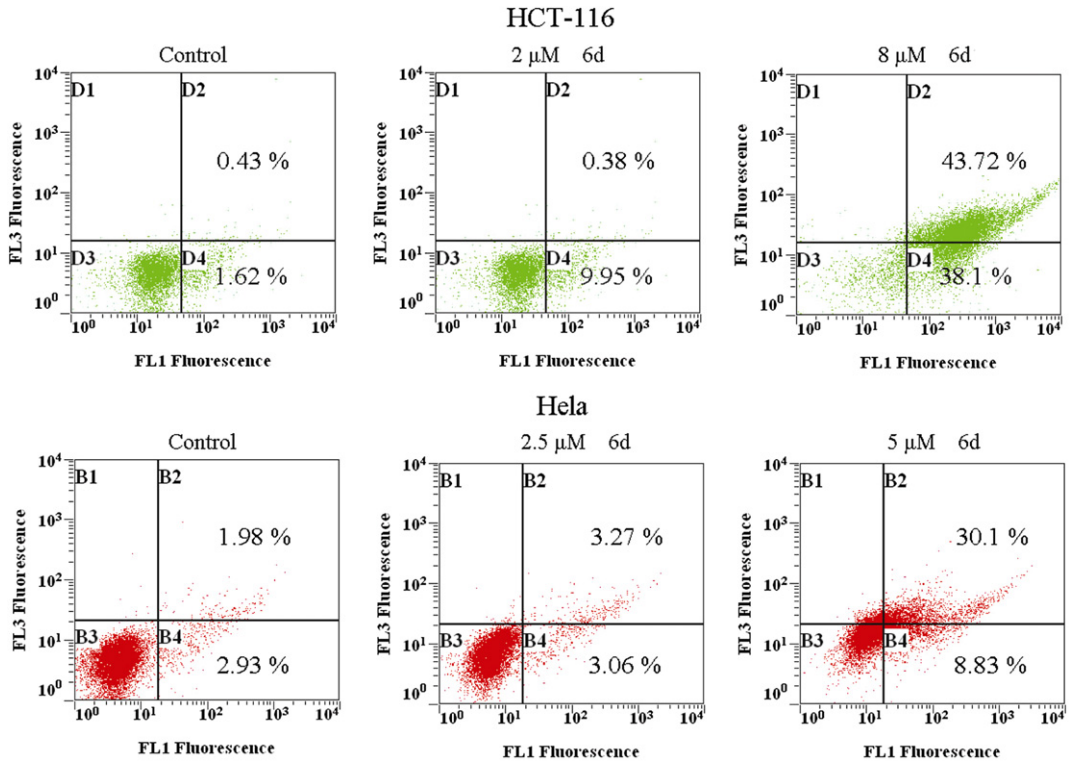


Fig. 2. Effects of compounds **6d** and **6n** on cell apoptosis of HCT-116 and Hela cells. Induction of apoptosis was measured by Annexin-V/PI double-staining assay after treatment with compounds **6d** (2, 8 μM) and **6n** (5, 10 μM) for 48 h. The profiles showed the apoptotic proportion of HCT-116 and Hela cells treated with compounds **6d** and **6n**, respectively.

4. Conclusion

In summary, we have synthesized 16 new formononetin nitrogen mustard derivatives, and evaluated their antitumor activities against five cell lines (HCT-116, SH-SY5Y, DU-145, Hela, SGC-7901). All the new compounds exhibited more potent inhibitory activity against HCT-116, SH-SY5Y and DU-145 than formononetin, and most of them displayed selective cytotoxicity toward SH-SY5Y cell line. Therefore, the introduction of nitrogen mustard at 3′-position in formononetin is associated with enhanced cytotoxic activity, especially when a cycloalkoxyl group is presented at the 7-position in formononetin. Our results also demonstrated that the cytotoxic activity of these new derivatives could be attributed to the induction of cell cycle arrest and apoptosis in cancer cells. This study might provide valuable clue for in search of more potent and selective antitumor agents based on the formononetin scaffold.

5. Experimental protocols

5.1. Synthesis

Reagents and solvents were purchased from commercial sources. Solvents were dried and purified using standard techniques. All reactions involving air or moisture sensitive reagents were performed under nitrogen atmosphere. NMR (^{1}H and ^{13}C) spectra were recorded on a Bruker AVANCE III; 500 Hz spectrometer. IR spectra were recorded on a Bruker Optics TENSOR 27 infrared spectrometer. Mass spectra were recorded on a Shimadzu VG-Autospec-3000 mass spectrometer.

5.1.1. 7-Hydroxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**2**)

A mixture of formononetin **1** (2.68 g, 10 mmol), glacial AcOH (100 mL), concentrated HNO_3 (0.788 g, 12.5 mmol), and concentrated H_2SO_4 (0.49 g, 5 mmol) was stirred at 50 °C for 12 h, and then the mixture was poured into ice water (200 mL). The resulting precipitated solid was filtered, washed with water, and crystallized from EtOH to give **2** as yellow powder (2.35 g, 75%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.97 (3H, s, OCH_3), 6.91 (1H, s, H-8), 6.97 (1H, d, J = 8.8 Hz, H-6), 7.44 (1H, d, J = 8.8 Hz, H-5′), 7.90 (1H, d, J = 9.2 Hz, H-6′), 7.99 (1H, d, J = 8.7 Hz, H-5), 8.15 (1H, s, H-2), 8.54 (1H, s, H-2); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 56.8 (OCH_3), 102.2 (C-8), 114.1 (C-6), 115.4 (C-5′), 116.4 (C-3), 121.0 (C-10), 124.4 (C-2′), 124.9 (C-1′), 127.3 (C-5), 134.6 (C-6′), 138.9 (C-3′), 151.5 (C-4′), 154.2 (C-2), 157.4 (C-9), 162.8 (C-7), 174.2 (C-4).

5.1.2. General procedures for preparation of ***3a*–*3l***

To a solution of 7-hydroxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one **2** (1.0 g, 3.2 mmol) in acetone (50 mL) were added R–Br (57.4 mmol) and K_2CO_3 (2.2 g, 16 mmol), and the reaction mixture was refluxed for 3–8 h. After cooling to room temperature, the solid was removed by suction filtration, and the filtrate was evaporated to dryness. Water (100 mL) was added to the residue, the resulting mixture was extracted with diethyl ether (3 × 50 mL), and the combined ethereal extracts were dried over anhydrous $MgSO_4$ and then concentrated *in vacuo*. The crude product was purified by crystallization from EtOH or column flash chromatography on silica gel to afford **3a**–**3l** as light yellow solid.

5.1.2.1. 7-Ethoxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (***3a***).

Yield 85%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.49 (3H, t, J = 7.0 Hz, CH_3), 4.00 (3H, s, OCH_3), 4.14 (2H, q, J = 7.0 Hz, CH_2), 6.86 (1H, d, J = 2.2 Hz, H-8), 6.99 (1H, dd, J = 6.7, 2.2 Hz, H-6), 7.16 (1H, d, J = 8.7 Hz, H-5′), 7.86 (1H, dd, J = 6.5, 2.1 Hz, H-6′), 7.99 (1H, s, H-2), 8.06 (1H, d, J = 2.1 Hz, H-2′), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.6 (CH_3), 56.7 (OCH_3), 64.4 (CH_2O), 100.7 (C-8), 113.6 (C-6), 115.3 (C-5′), 118.0 (C-3), 122.9 (C-10), 124.6 (C-1′),

125.8 (C-2′), 127.7 (C-5), 135.0 (C-6′), 139.5 (C-3′), 152.6 (C-2), 152.8 (C-4′), 158.0 (C-9), 163.7 (C-7), 175.3 (C-4).

*5.1.2.2. 7-Propoxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3b**).* Yield 84%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.08 (3H, t, J = 7.0 Hz, CH_3), 1.86–1.90 (2H, m, CH_2), 4.00 (3H, s, OCH_3), 4.03 (2H, t, J = 6.5 Hz, OCH_2), 6.86 (1H, d, J = 2.0 Hz, H-8), 7.01 (1H, dd, J = 6.5, 2.5 Hz, H-6), 7.16 (1H, d, J = 9.0 Hz, H-5′), 7.86 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.99 (1H, s, H-2), 8.06 (1H, d, J = 2.0 Hz, H-2′), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.5 (CH_3), 22.4 (CH_2), 56.7 (OCH_3), 70.3 (CH_2O), 100.7 (C-8), 113.6 (C-6), 115.3 (C-5′), 118.0 (C-3), 122.9 (C-10), 124.6 (C-1′), 125.8 (C-2′), 127.7 (C-5), 135.0 (C-6′), 139.5 (C-3′), 152.6 (C-2), 152.8 (C-4′), 158.0 (C-9), 163.9 (C-7), 175.3 (C-4).

*5.1.2.3. 7-Butoxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3c**).* Yield 83%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.00 (3H, t, J = 7.3 Hz, CH_3), 1.51–1.55 (2H, m, γ-CH_2), 1.81–1.86 (2H, m, β-CH_2), 4.00 (3H, s, OCH_3), 4.08 (2H, t, J = 6.5 Hz, OCH_2), 6.86 (1H, d, J = 2.0 Hz, H-8), 7.01 (1H, dd, J = 6.5, 2.5 Hz, H-6), 7.15 (1H, d, J = 9.0 Hz, H-5′), 7.85 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.99 (1H, s, H-2), 8.06 (1H, d, J = 2.0 Hz, H-2′), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.7 (CH_3), 19.2 (CH_2), 31.0 (CH_2), 56.7 (OCH_3), 68.6 (CH_2O), 100.7 (C-8), 113.6 (C-6), 115.3 (C-5′), 118.0 (C-3), 122.9 (C-10), 124.6 (C-1′), 125.8 (C-2′), 127.7 (C-5), 134.9 (C-6′), 139.6 (C-3′), 152.6 (C-2), 152.8 (C-4′), 158.0 (C-9), 164.0 (C-7), 175.3 (C-4).

*5.1.2.4. 7-Isopropoxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3d**).* Yield 84%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.42 (6H, d, J = 6.0 Hz, $2CH_3$), 4.00 (3H, s, OCH_3), 4.64–4.69 (1H, m, OCH), 6.86 (1H, d, J = 2.2 Hz, H-8), 6.98 (1H, dd, J = 6.6, 2.2 Hz, H-6), 7.16 (1H, d, J = 8.7 Hz, H-5′), 7.86 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.99 (1H, s, H-2), 8.05 (1H, d, J = 2.0 Hz, H-2′), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.8 ($2CH_3$), 56.7 (OCH_3), 70.9 (CHO), 101.7 (C-8), 113.6 (C-6), 115.3 (C-5′), 117.8 (C-3), 122.8 (C-10), 124.6 (C-1′), 125.8 (C-2′), 127.7 (C-5), 134.9 (C-6′), 139.5 (C-3′), 152.6 (C-2), 152.8 (C-4′), 158.1 (C-9), 162.8 (C-7), 175.3 (C-4).

*5.1.2.5. 7-sec-Butoxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3e**).* Yield 82%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.01 (3H, t, J = 7.0 Hz, β-CH_3), 1.37 (3H, d, J = 6.0 Hz, α-CH_3), 1.69–1.74 (2H, m, CH_2), 4.00 (3H, s, OCH_3), 4.41–4.47 (H, m, OCH), 6.85 (1H, d, J = 2.5 Hz, H-8), 6.98 (1H, dd, J = 6.5, 2.5 Hz, H-6), 7.15 (1H, d, J = 9.0 Hz, H-5′), 7.85 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.99 (1H, s, H-2), 8.06 (1H, d, J = 2.0 Hz, H-2′), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.7 (β-CH_3), 19.0 (α-CH_3), 29.0 (CH_2), 56.7 (OCH_3), 76.0 (CHO), 101.7 (C-8), 113.6 (C-6), 115.9 (C-5′), 117.8 (C-3), 122.8 (C-10), 124.7 (C-1′), 125.8 (C-2′), 127.8 (C-5), 134.9 (C-6′), 139.6 (C-3′), 152.6 (C-2), 152.8 (C-4′), 158.1 (C-9), 163.1 (C-7), 175.2 (C-4).

*5.1.2.6. 7-(Pentan-2-yloxy)-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3f**).* Yield 80%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.00 (6H, d, J = 7.0 Hz, $2CH_3$), 1.75 (2H, q, J = 6.5 Hz, CH_2), 1.83–1.89 (1H, m, CH), 4.00 (3H, s, OCH_3), 4.10 (2H, t, J = 6.5 Hz, OCH_2), 6.86 (1H, d, J = 2.5 Hz, H-8), 7.00 (1H, dd, J = 7.0, 2.0 Hz, H-6), 7.15 (1H, d, J = 8.5 Hz, H-5′), 7.85 (1H, dd, J = 6.5, 2.5 Hz, H-6′), 7.99 (1H, s, H-2), 8.06 (1H, d, J = 2.0 Hz, H-2′), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.6 ($2CH_3$), 25.1 (CH), 37.7 (CH_2), 56.7 (OCH_3), 67.3 (CH_2O), 100.7 (C-8), 113.6 (C-6), 115.4 (C-5′), 118.0 (C-3), 122.9 (C-10), 124.6 (C-1′), 125.9 (C-2′), 127.7 (C-5), 135.0 (C-6′), 139.6 (C-3′), 152.7 (C-2), 152.9 (C-4′), 158.1 (C-9), 164.0 (C-7), 175.3 (C-4).

*5.1.2.7. 7-Allyloxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3g**).* Yield 87%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.00 (3H, s, OCH_3), 4.66 (2H, t, J = 5.5 Hz, OCH_2), 5.37 (1H, dd, J = 9.5, 1.0 Hz, $\underline{CH_2}$=CH), 5.47 (1H, dd, J = 17.0, 1.5 Hz, $\underline{CH_2}$=CH), 6.04–6.11 (1H, m, CH), 6.89 (1H, d, J = 2.0 Hz, H-8), 7.04 (1H, dd, J = 6.5, 2.5 Hz, H-6), 7.16 (1H, d, J = 9.0 Hz, H-5′), 7.86 (1H, dd, J = 6.5, 2.5 Hz, H-6′), 8.00 (1H, s, H-2), 8.06 (1H, d, J = 2.0 Hz, H-2′), 8.20 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 56.7 (OCH_3), 69.3 (CH_2O), 101.2 (C-8), 113.6 (C-6), 115.4 (C-5′), 118.2 (C-3), 118.7 (CH), 122.9 (C-10), 124.5 (C-1′), 125.8 (C-2′), 127.8 (C-5), 132.0 ($\underline{CH_2}$=CH), 135.0 (C-6′), 139.5 (C-3′), 152.6 (C-2), 152.8 (C-4′), 157.9 (C-9), 163.2 (C-7), 175.3 (C-4).

*5.1.2.8. 7-(2-Methylallyloxy)-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3h**).* Yield 84%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.86 (3H, s, CH_3), 3.99 (3H, s, OCH_3), 4.55 (2H, s, OCH_2), 5.06 (1H, s, $\underline{CH_2}$=C), 5.13 (1H, s, $\underline{CH_2}$=C), 6.88 (1H, d, J = 2.0 Hz, H-8), 7.04 (1H, dd, J = 6.5, 2.5 Hz, H-6), 7.15 (1H, d, J = 8.5 Hz, H-5′), 7.83 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.99 (1H, s, H-2), 8.06 (1H, d, J = 2.0 Hz, H-2′), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.3 (CH_3), 56.7 (OCH_3), 72.3 (CH_2O), 101.2 (C-8), 113.6 (C-6), 113.7 ($\underline{CH_2}$=C), 115.4 (C-5′), 118.2 (C-3), 122.9 (C-10), 124.5 (C-1′), 125.8 (C-2′), 127.7 (C-5), 135.0 (C-6′), 139.5 (C-3′), 139.7 (CH_2=$\underline{C}$), 152.6 (C-2), 152.8 (C-4′), 157.9 (C-9), 163.4 (C-7), 175.2 (C-4).

*5.1.2.9. 7-(3-Methylbut-2-enyloxy)-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3i**).* Yield 85%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.80 (3H, s, CH_3), 1.82 (3H, s, CH_3), 4.00 (3H, s, OCH_3), 4.63 (2H, d, J = 6.5 Hz, OCH_2), 5.51 (1H, t, J = 6.5 Hz, $\underline{CH}$=C), 6.88 (1H, d, J = 2.5 Hz, H-8), 7.02 (1H, dd, J = 6.5, 2.5 Hz, H-6), 7.16 (1H, d, J = 8.5 Hz, H-5′), 7.86 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.99 (1H, s, H-2), 8.06 (1H, d, J = 2.5 Hz, H-2′), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 17.3 (CH_3), 24.8 (CH_3), 55.7 (OCH_3), 64.6 (CH_2O), 100.0 (C-8), 112.6 (C-6), 114.4 (C-5′), 117.0 (C-3), 117.5 ($\underline{CH}$=C), 121.9 (C-10), 123.6 (C-1′), 124.8 (C-2′), 126.7 (C-5), 133.9 (C-6′), 138.5 (C-3′), 138.7 (CH=$\underline{C}$), 151.6 (C-2), 151.8 (C-4′), 157.0 (C-9), 162.6 (C-7), 174.3 (C-4).

*5.1.2.10. 7-Benzyloxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3j**).* Yield 86%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.00 (3H, s, OCH_3), 5.19 (2H, s, OCH_2), 6.96 (1H, d, J = 2.5 Hz, H-8), 7.09 (1H, dd, J = 6.5, 2.5 Hz, H-6), 7.16 (1H, d, J = 8.8 Hz, H-5′), 7.43–7.45 (5H, m, Ph-H), 7.86 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.99 (1H, s, H-2), 8.05 (1H, d, J = 2.0 Hz, H-2′), 8.21 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 56.7 (OCH_3), 70.7 (CH_2O), 101.4 (C-8), 113.6 (C-6), 115.4 (C-5′), 118.4 (C-3), 122.9 (C-10), 124.5 (C-1′), 125.8 (C-2′), 127.5 (2o-Ph-C), 127.8 (C-5), 128.8 (p-Ph-C), 128.9 (2m-Ph-C), 134.9 (C-6′), 135.6 (Ph-C), 139.6 (C-3′), 152.6 (C-2), 152.9 (C-4′), 157.9 (C-9), 163.4 (C-7), 175.2 (C-4).

*5.1.2.11. 7-Phenethoxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3k**).* Yield 79%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.17 (2H, t, J = 7.0 Hz, CH_2Ph), 4.00 (3H, s, OCH_3), 4.28 (2H, t, J = 7.5 Hz, OCH_2), 6.86 (1H, d, J = 2.0 Hz, H-8), 7.01 (1H, dd, J = 7.0, 2.0 Hz, H-6), 7.15 (1H, d, J = 8.5 Hz, H-5′), 7.27–7.37 (5H, m, 5 × Ph-H), 7.85 (1H, dd, J = 6.5, 2.5 Hz, H-6′), 7.98 (1H, s, H-2), 8.05 (1H, d, J = 2.0 Hz, H-2′), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.6 (CH_2), 56.7 (OCH_3), 69.5 (CH_2O), 100.9 (C-8), 113.7 (C-6), 115.4 (C-5′), 118.2 (C-3), 122.9 (C-10), 124.6 (C-1′), 125.9 (C-2′), 126.9 (A_4-C), 127.8 (C-5), 128.7 (2 × A_2-C), 129.1 (2 × A_3-C), 135.1 (C-6′), 137.6 (A_1-C), 139.5 (C-3′), 152.7 (C-2), 152.9 (C-4′), 158.0 (C-9), 163.4 (C-7), 175.3 (C-4).

*5.1.2.12. 7-(4-Methylbenzyloxy)-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3l**).* Yield 83%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.38 (3H, s, CH_3), 4.00 (3H, s, OCH_3), 5.14 (2H, s, OCH_2), 6.95 (1H, d, J = 2.0 Hz, H-8), 7.07 (1H, dd, J = 7.0, 2.0 Hz, H-6), 7.16 (1H, d, J = 8.8 Hz, H-5′), 7.22 (2H, d, J = 9.5 Hz, 2 × A_3-H), 7.34 (2H, d, J = 9.5 Hz, 2 × A_2-H), 7.85 (1H, dd, J = 6.5, 2.5 Hz, H-6′), 7.98 (1H, s, H-2), 8.05 (1H, d, J = 2.0 Hz, H-2′), 8.20 (1H, d, J = 9.0 Hz, H-5); ^{13}C

NMR ($CDCl_3$, 125 MHz): δ 21.2 (CH_3), 56.7 (OCH_3), 70.6 (CH_2O), 101.4 (C-8), 113.6 (C-6), 115.5 (C-5′), 118.3 (C-3), 122.9 (C-10), 124.5 (C-1′), 125.8 (C-2′), 127.7 (2 × A_2-C), 127.8 (C-5), 129.5 (2 × A_3-C), 132.5 (A_4-C), 135.0 (C-6′), 138.4 (A_1-C), 139.5 (C-3′), 152.6 (C-2), 152.8 (C-4′), 157.9 (C-9), 163.4 (C-7), 175.2 (C-4).

5.1.3. General procedure for preparation of ***3m–3o***

To an ice-cold stirred solution of 7-hydroxy-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one **2** (1.0 g, 3.2 mmol), cycloalkanol (6.4 mmol), PPh_3 (6.4 mmol) and anhydrous THF (50 mL) were added dropwise diisopropyl azodicarboxylate (DIAD) (6.4 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then allowed to warm to rt, continuing stirring overnight. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography to afford **3m–3o** as light yellow solid.

*5.1.3.1. 7-(Cyclopentyloxy)-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3m**).* Yield 77%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.63–2.05 (8H, m, 4 × CH_2), 4.00 (3H, s, OCH_3), 4.85–4.88 (1H, m, CH), 6.84 (1H, d, *J* = 2.0 Hz, H-8), 6.97 (1H, dd, *J* = 7.0, 2.0 Hz, H-6), 7.15 (1H, d, *J* = 9.0 Hz, H-5′), 7.86 (1H, dd, *J* = 6.5, 2.0 Hz, H-6′), 7.99 (1H, s, H-2), 8.05 (1H, d, *J* = 2.5 Hz, H-2′), 8.17 (1H, d, *J* = 8.5 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.1 (2β-CH_2), 32.8 (2α-CH_2), 56.7 (OCH_3), 80.4 (CHO), 101.6 (C-8), 113.6 (C-6), 116.0 (C-5′), 117.7 (C-3), 122.8 (C-10), 124.6 (C-1′), 125.8 (C-2′), 127.6 (C-5), 135.0 (C-6′), 139.5 (C-3′), 152.6 (C-2), 152.8 (C-4′), 158.0 (C-9), 163.0 (C-7), 175.3 (C-4).

*5.1.3.2. 7-(Cyclohexyloxy)-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3n**).* Yield 71%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.35–2.02 (10H, m, 5 × CH_2), 4.00 (3H, s, OCH_3), 4.35–4.37 (1H, m, CH), 6.86 (1H, d, *J* = 2.0 Hz, H-8), 6.99 (1H, dd, *J* = 7.0, 2.0 Hz, H-6), 7.15 (1H, d, *J* = 8.5 Hz, H-5′), 7.85 (1H, dd, *J* = 6.5, 2.0 Hz, H-6′), 7.98 (1H, s, H-2), 8.05 (1H, d, *J* = 2.5 Hz, H-2′), 8.17 (1H, d, *J* = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.6 (2 × CH_2), 25.5 (CH_2), 31.5 (2 × CH_2), 56.7 (OCH_3), 76.2 (CH), 101.9 (C-8), 113.6 (C-6), 116.0 (C-5′), 117.9 (C-3), 122.9 (C-10), 124.7 (C-1′), 125.8 (C-2′), 127.8 (C-5), 135.0 (C-6′), 139.6 (C-3′), 152.5 (C-2), 152.8 (C-4′), 158.1 (C-9), 162.8 (C-7), 175.2 (C-4).

*5.1.3.3. 7-(Cycloheptyloxy)-3-(4-methoxy-3-nitrophenyl)-4H-chromen-4-one (**3o**).* Yield 65%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.52–2.09 (12H, m, 6 × CH_2), 4.00 (3H, s, OCH_3), 4.53–4.56 (1H, m, CH), 6.81 (1H, d, *J* = 2.0 Hz, H-8), 6.96 (1H, dd, *J* = 6.5, 2.5 Hz, H-6), 7.15 (1H, d, *J* = 8.5 Hz, H-5′), 7.85 (1H, dd, *J* = 6.5, 2.0 Hz, H-6′), 7.98 (1H, s, H-2), 8.05 (1H, d, *J* = 2.0 Hz, H-2′), 8.17 (1H, d, *J* = 8.5 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.9 (2 × CH_2), 28.3 (2 × CH_2), 33.5 (2 × CH_2), 56.7 (OCH_3), 78.8 (CH), 101.8 (C-8), 113.6 (C-6), 116.1 (C-5′), 117.7 (C-3), 122.8 (C-10), 124.6 (C-1′), 125.8 (C-2′), 127.7 (C-5), 135.0 (C-6′), 139.5 (C-3′), 152.5 (C-2), 152.8 (C-4′), 158.1 (C-9), 162.8 (C-7), 175.3 (C-4).

5.1.4. General procedure for preparation of ***4a–4o***

A mixture of compounds **3a–3o** (500 mg), Zn powder (2.5 equiv), AcOH (0.2 mL) and EtOH (30 mL) was refluxed for 1–2 h, and the solvents were evaporated to dryness *in vacuo*, and then DCM (30 mL) was added to the residue. The mixture was filtered and the filtrate was concentrated *in vacuo* to get crud product, which was purified by flash chromatography on silica gel (EtOAc:petroleum ether = 1:4) to give compounds **4a–4o** as white powder.

*5.1.4.1. 7-Ethoxy-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4a**).* Yield 85%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.48 (3H, t, *J* = 7.0 Hz, CH_3), 3.88 (3H, s, OCH_3), 4.14 (2H, q, *J* = 7.0 Hz, CH_2), 6.82 (1H, d, *J* = 2.0 Hz, H-8), 6.84 (1H, d, *J* = 8.5 Hz, H-5′), 6.89 (1H, dd, *J* = 6.5, 2.0 Hz, H-6′), 6.96 (1H, dd, *J* = 7.0, 2.0 Hz, H-6), 6.98 (1H, d, *J* = 2.0 Hz, H-2′), 7.89 (1H, s, H-2), 8.19 (1H, d, *J* = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.6 (CH_3), 55.6 (OCH_3), 64.2 (CH_2O), 100.5 (C-8), 110.3 (C-2′), 114.7 (C-6), 115.8 (C-5′), 118.3 (C-3), 119.0 (C-6′), 124.7 (C-10), 125.1 (C-1′), 127.8 (C-5), 136.1 (C-3′), 147.4 (C-4′), 152.1 (C-2), 157.9 (C-9), 163.3 (C-7), 175.9 (C-4).

*5.1.4.2. 7-Propoxy-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4b**).* Yield 83%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.09 (3H, t, *J* = 7.5 Hz, CH_3), 1.86–1.90 (2H, m, CH_2), 3.87 (3H, s, OCH_3), 4.01 (2H, t, *J* = 7.0 Hz, OCH_2), 6.82 (1H, d, *J* = 1.5 Hz, H-8), 6.83 (1H, d, *J* = 7.5 Hz, H-5′), 6.88 (1H, dd, *J* = 6.5, 2.0 Hz, H-6′), 6.97 (1H, dd, *J* = 7.0, 2.0 Hz, H-6), 6.98 (1H, d, *J* = 2.0 Hz, H-2′), 7.89 (1H, s, H-2), 8.19 (1H, d, *J* = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.5 (CH_3), 22.4 (CH_2), 55.7 (OCH_3), 70.2 (CH_2O), 100.7 (C-8), 110.5 (C-2′), 114.9 (C-6), 115.9 (C-5′), 118.4 (C-3), 119.0 (C-6′), 124.8 (C-10), 125.2 (C-1′), 127.8 (C-5), 136.2 (C-3′), 147.5 (C-4′), 152.1 (C-2), 157.9 (C-9), 163.5 (C-7), 176.0 (C-4).

*5.1.4.3. 7-Butoxy-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4c**).* Yield 84%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.00 (3H, t, *J* = 7.5 Hz, CH_3), 1.50–1.55 (2H, m, γ-CH_2), 1.79–1.84 (2H, m, β-CH_2), 3.87 (3H, s, OCH_3), 4.05 (2H, t, *J* = 6.5 Hz, OCH_2), 6.82 (1H, d, *J* = 2.0 Hz, H-8), 6.83 (1H, d, *J* = 8.0 Hz, H-5′), 6.88 (1H, dd, *J* = 6.5, 2.0 Hz, H-6′), 6.96 (1H, dd, *J* = 7.0, 2.0 Hz, H-6), 6.97 (1H, d, *J* = 2.0 Hz, H-2′), 7.89 (1H, s, H-2), 8.18 (1H, d, *J* = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.7 (CH_3), 19.2 (γ-CH_2), 31.0 (β-CH_2), 55.6 (OCH_3), 68.4 (CH_2O), 100.6 (C-8), 110.4 (C-2′), 114.8 (C-6), 115.8 (C-5′), 118.3 (C-3), 119.0 (C-6′), 124.8 (C-10), 125.2 (C-1′), 127.7 (C-5), 136.2 (C-3′), 147.5 (C-4′), 152.1 (C-2), 157.9 (C-9), 163.5 (C-7), 175.9 (C-4).

*5.1.4.4. 7-Isopropoxy-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4d**).* Yield 80%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.40 (6H, d, *J* = 6.0 Hz, 2 × CH_3), 3.88 (3H, s, OCH_3), 4.63–4.69 (1H, m, OCH), 6.81 (1H, d, *J* = 2.0 Hz, H-8), 6.83 (1H, d, *J* = 7.5 Hz, H-5′), 6.88 (1H, dd, *J* = 6.0, 2.0 Hz, H-6′), 6.94 (1H, dd, *J* = 6.5, 2.5 Hz, H-6), 6.97 (1H, d, *J* = 2.0 Hz, H-2′), 7.89 (1H, s, H-2), 8.18 (1H, d, *J* = 8.5 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.9 (2 × CH_3), 55.7 (OCH_3), 70.8 (CHO), 101.6 (C-8), 110.5 (C-2′), 115.5 (C-6), 115.9 (C-5′), 118.3 (C-3), 119.1 (C-6′), 124.9 (C-10), 125.2 (C-1′), 127.9 (C-5), 136.2 (C-3′), 147.5 (C-4′), 152.1 (C-2), 158.0 (C-9), 162.4 (C-7), 175.9 (C-4).

*5.1.4.5. 7-sec-Butoxy-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4e**).* Yield 80%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.01 (3H, t, *J* = 7.5 Hz, β-CH_3), 1.36 (3H, d, *J* = 6.0 Hz, α-CH_3), 1.69–1.74 (2H, m, CH_2), 3.88 (3H, s, OCH_3), 4.40–4.47 (H, m, OCH), 6.81 (1H, d, *J* = 2.5 Hz, H-8), 6.83 (1H, d, *J* = 7.5 Hz, H-5′), 6.88 (1H, dd, *J* = 6.5, 2.0 Hz, H-6′), 6.95 (1H, dd, *J* = 6.5, 2.5 Hz, H-6), 6.97 (1H, d, *J* = 2.0 Hz, H-2′), 7.89 (1H, s, H-2), 8.18 (1H, d, *J* = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.8 (β-CH_3), 19.1 (α-CH_3), 29.1 (CH_2), 55.7 (OCH_3), 75.8 (CHO), 101.6 (C-8), 110.4 (C-2′), 115.5 (C-6), 115.8 (C-5′), 118.2 (C-3), 119.1 (C-6′), 124.8 (C-10), 125.1 (C-1′), 127.9 (C-5), 136.1 (C-3′), 147.5 (C-4′), 152.1 (C-2), 158.0 (C-9), 162.7 (C-7), 176.0 (C-4).

*5.1.4.6. 7-(Pentan-2-yloxy)-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4f**).* Yield 78%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (6H, d, *J* = 6.5 Hz, 2 × CH_3), 1.73 (2H, q, *J* = 6.5 Hz, CH_2), 1.83–1.89 (1H, m, CH), 3.87 (3H, s, OCH_3), 4.07 (2H, t, *J* = 6.5 Hz, OCH_2), 6.82 (1H, d, *J* = 2.5 Hz, H-8), 6.83 (1H, d, *J* = 8.0 Hz, H-5′), 6.88 (1H, dd, *J* = 6.0, 2.0 Hz, H-6′), 6.95 (1H, dd, *J* = 7.5, 2.5 Hz, H-6), 6.97 (1H, d, *J* = 1.5 Hz, H-2′), 7.88 (1H, s, H-2), 8.18 (1H, d, *J* = 8.5 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.5 (2 × CH_3), 25.1 (CH), 37.7 (CH_2), 55.5 (OCH_3), 67.1 (CH_2O), 100.6 (C-8), 110.4 (C-2′), 114.8 (C-6), 115.8 (C-5′), 118.3 (C-3), 119.0 (C-6′), 124.8 (C-10), 125.1 (C-1′), 127.7 (C-5),

136.2 (C-3′), 147.5 (C-4′), 152.1 (C-2), 157.9 (C-9), 163.5 (C-7), 175.9 (C-4).

*5.1.4.7. 7-Allyloxy-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4g**).* Yield 80%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (3H, s, OCH_3), 4.63 (2H, t, J = 5.5 Hz, OCH_2), 5.35 (1H, dd, J = 9.5, 1.0 Hz, $\underline{CH_2}$=CH), 5.47 (1H, dd, J = 16.0, 1.5 Hz, $\underline{CH_2}$=CH), 6.03–6.10 (1H, m, CH), 6.82 (1H, d, J = 8.0 Hz, H-5′), 6.84 (1H, d, J = 2.5 Hz, H-8), 6.87 (1H, dd, J = 6.0, 2.0 Hz, H-6′), 6.97 (1H, d, J = 2.0 Hz, H-2′), 7.00 (1H, dd, J = 6.5, 2.5 Hz, H-6), 7.89 (1H, s, H-2), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 55.6 (OCH_3), 69.3 (CH_2O), 101.1 (C-8), 110.4 (C-2′), 114.9 (C-6), 115.8 (C-5′), 118.6 (CH), 118.6 (C-3), 119.1 (C-6′), 124.7 (C-10), 125.2 (C-1′), 127.9 (C-5), 132.2 ($\underline{CH_2}$=CH), 136.2 (C-3′), 147.5 (C-4′), 152.2 (C-2), 157.8 (C-9), 162.9 (C-7), 175.9 (C-4).

*5.1.4.8. 7-(2-Methylallyloxy)-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4h**).* Yield 81%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.85 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 4.53 (2H, s, OCH_2), 5.05 (1H, s, $\underline{CH_2}$=C), 5.12 (1H, s, $\underline{CH_2}$=C), 6.82 (1H, d, J = 8.5 Hz, H-5′), 6.84 (1H, d, J = 2.5 Hz, H-8), 6.88 (1H, dd, J = 6.0, 2.0 Hz, H-6′), 6.97 (1H, d, J = 2.0 Hz, H-2′), 7.00 (1H, dd, J = 7.0, 2.5 Hz, H-6), 7.89 (1H, s, H-2), 8.19 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.3 (CH_3), 55.6 (OCH_3), 72.2 (CH_2O), 101.0 (C-8), 110.4 (C-2′), 113.5 ($\underline{CH_2}$=C), 114.9 (C-6), 115.8 (C-5′), 118.5 (C-3), 119.0 (C-6′), 124.7 (C-10), 125.2 (C-1′), 127.8 (C-5), 136.1 (C-3′), 139.8 (CH_2=$\underline{C}$), 147.4 (C-4′), 152.1 (C-2), 157.8 (C-9), 163.0 (C-7), 175.9 (C-4).

*5.1.4.9. 7-(3-Methylbut-2-enyloxy)-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4i**).* Yield 79%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.80 (3H, s, CH_3), 1.82 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 4.60 (2H, d, J = 7.0 Hz, OCH_2), 5.50 (1H, t, J = 7.0 Hz, $\underline{CH}$=C), 6.82 (1H, d, J = 8.0 Hz, H-5′), 6.84 (1H, d, J = 2.5 Hz, H-8), 6.88 (1H, dd, J = 6.0, 2.0 Hz, H-6′), 6.97 (1H, d, J = 2.5 Hz, H-2′), 6.98 (1H, dd, J = 7.0, 2.5 Hz, H-6), 7.89 (1H, s, H-2), 8.19 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.3 (CH_3), 25.8 (CH_3), 55.6 (OCH_3), 65.4 (CH_2O), 100.8 (C-8), 110.3 (C-2′), 114.9 (C-5), 115.8 (C-5′), 118.3 (C-3), 118.6 ($\underline{CH}$=C), 119.0 (C-6′), 124.7 (C-10), 125.1 (C-1′), 127.7 (C-9), 136.1 (C-3′), 139.3 (CH=$\underline{C}$), 147.4 (C-4′), 152.1 (C-2), 157.8 (C-9), 163.1 (C-7), 175.9 (C-4).

*5.1.4.10. 7-(Benzyloxy)-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4j**).* Yield 85%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (3H, s, OCH_3), 5.16 (2H, s, OCH_2), 6.82 (1H, d, J = 8.5 Hz, H-5′), 6.87 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 6.91 (1H, d, J = 2.0 Hz, H-8), 6.97 (1H, d, J = 1.5 Hz, H-2′), 7.05 (1H, dd, J = 6.5, 2.5 Hz, H-6), 7.36–7.45 (5H, m, Ph-H), 7.88 (1H, s, H-2), 8.21 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 54.6 (OCH_3), 69.5 (CH_2O), 100.2 (C-8), 109.4 (C-2′), 113.9 (C-6), 114.8 (C-5′), 117.7 (C-3), 118.0 (C-6′), 123.7 (C-10), 124.2 (C-1′), 126.5 (2 × A_2-C), 126.9 (C-5), 127.4 (A_4-C), 127.8 (2 × A_3-C), 134.9 (C-3′), 135.1 (A_1-C), 146.5 (C-4′), 151.0 (C-2), 156.8 (C-9), 161.9 (C-7), 174.8 (C-4).

*5.1.4.11. 7-Phenethoxy-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4k**).* Yield 79%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.17(2H, t, J = 7.0 Hz, CH_2Ph), 3.87 (3H, s, OCH_3), 4.28 (2H, t, J = 7.5 Hz, OCH_2), 6.82 (1H, d, J = 2.0 Hz, H-8), 6.83 (1H, d, J = 6.5 Hz, H-5′), 6.88 (1H, dd, J = 8.5, 2.0 Hz, H-6′), 6.96 (1H, dd, J = 6.5, 2.5 Hz, H-6), 6.97 (1H, d, J = 2.5 Hz, H-2′), 7.25–7.36 (5H, m, 5 × Ph-H), 7.88 (1H, s, H-2), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.6 (CH_2), 55.6 (OCH_3), 69.3 (CH_2O), 100.7 (C-8), 110.4 (C-2′), 114.8 (C-6), 115.8 (C-5′), 118.5 (C-3), 119.1 (C-6′), 124.7 (C-10), 125.2 (C-1′), 126.8 (A_4-C), 127.8 (C-5), 128.7 (2 × A_2-C), 129.1 (2 × A_3-C), 136.1 (C-3′), 137.7 (A_1-C), 147.5 (C-4′), 152.2 (C-2), 157.8 (C-9), 163.1 (C-7), 175.9 (C-4).

*5.1.4.12. 7-(4-Methylbenzyloxy)-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4l**).* Yield 84%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.38 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 5.14 (2H, s, OCH_2), 6.82 (1H, d, J = 8.0 Hz, H-5′), 6.86 (1H, d, J = 2.5 Hz, H-8), 6.90 (1H, dd, J = 6.5, 2.5 Hz, H-6′), 6.96 (1H, d, J = 2.0 Hz, H-2′), 7.04 (1H, dd, J = 6.5, 2.5 Hz, H-6), 7.22 (2H, d, J = 8.0 Hz, 2 × A_3-H), 7.33 (2H, d, J = 7.5 Hz, 2 × A_2-H), 7.87 (1H, s, H-2), 8.20 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.2 (CH_3), 55.6 (OCH_3), 70.6 (CH_2O), 101.2 (C-8), 110.4 (C-2′), 114.9 (C-6), 115.8 (C-5′), 118.6 (C-3), 119.1 (C-6′), 124.8 (C-10), 125.2 (C-1′), 127.8 (2 × A_2-C), 127.9 (C-5), 129.5 (2 × A_3-C), 132.5 (A_4-C), 136.1 (A_1-C), 138.3 (C-3′), 147.5 (C-4′), 152.2 (C-2), 157.8 (C-9), 163.1 (C-7), 175.9 (C-4).

*5.1.4.13. 7-Cyclopentyloxy-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4m**).* Yield 84%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.63–2.01 (8H, m, 4 × CH_2), 3.87 (3H, s, OCH_3), 4.83–4.86 (1H, m, CH), 6.80 (1H, d, J = 2.0 Hz, H-8), 6.83 (1H, d, J = 8.5 Hz, H-5′), 6.88 (1H, dd, J = 6.0, 2.0 Hz, H-6′), 6.93 (1H, dd, J = 6.5, 2.5 Hz, H-6), 6.97 (1H, d, J = 2.0 Hz, H-2′), 7.88 (1H, s, H-2), 8.17 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.1 (2 × CH_2), 32.8 (2 × CH_2), 55.6 (OCH_3), 80.2 (CHO), 101.5 (C-8), 110.4 (C-2′), 115.5 (C-6), 115.8 (C-5′), 118.0 (C-3), 119.0 (C-6′), 124.8 (C-10), 125.1 (C-1′), 127.7 (C-5), 136.1 (C-3′), 147.4 (C-4′), 152.0 (C-2), 157.8 (C-9), 162.5 (C-7), 175.9 (C-4).

*5.1.4.14. 7-Cyclohexyloxy-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4n**).* Yield 83%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.35–2.03 (10H, m, 5 × CH_2), 3.86 (3H, s, OCH_3), 4.35–4.37 (1H, m, CH), 6.82 (1H, d, J = 2.5 Hz, H-8), 6.83 (1H, d, J = 7.0 Hz, H-5′), 6.88 (1H, dd, J = 6.0, 2.0 Hz, H-6′), 6.94 (1H, dd, J = 7.0, 2.5 Hz, H-6), 6.97 (1H, d, J = 2.0 Hz, H-2′), 7.87 (1H, s, H-2), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.6 (2 × CH_2), 25.5 (CH_2), 31.5 (2 × CH_2), 55.6 (OCH_3), 76.0 (CH), 101.6 (C-8), 110.3 (C-2′), 115.5 (C-6), 115.8 (C-5′), 118.1 (C-3), 119.0 (C-6′), 124.8 (C-10), 125.1 (C-1′), 127.7 (C-5), 136.1 (C-3′), 147.4 (C-4′), 152.0 (C-2), 157.9 (C-9), 162.2 (C-7), 175.9 (C-4).

*5.1.4.15. 7-Cycloheptyloxy-3-(3-amino-4-methoxyphenyl)-4H-chromen-4-one (**4o**).* Yield 82%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.52–2.09 (12H, m, 6 × CH_2), 3.87 (3H, s, OCH_3), 4.51–4.54 (1H, m, CH), 6.77 (1H, d, J = 2.0 Hz, H-8), 6.83 (1H, d, J = 8.5 Hz, H-5′), 6.88 (1H, dd, J = 6.0, 2.0 Hz, H-6′), 6.93 (1H, dd, J = 7.0, 2.0 Hz, H-6), 6.97 (1H, d, J = 2.0 Hz, H-2′), 7.88 (1H, s, H-2), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.9 (2 × CH_2), 28.3 (2 × CH_2), 33.5 (2 × CH_2), 55.6 (OCH_3), 78.6 (CH), 101.6 (C-8), 110.3 (C-2′), 115.6 (C-6), 115.8 (C-5′), 118.1 (C-3), 119.0 (C-6′), 124.8 (C-10), 125.1 (C-1′), 127.8 (C-5), 136.1 (C-3′), 147.4 (C-4′), 152.0 (C-2), 157.9 (C-9), 162.3 (C-7), 175.9 (C-4).

*5.1.5. General procedure for preparation of **5a**–**5o***

To an ice-cold stirred solution of compounds **4a**–**4o** (300 mg) dissolved in AcOH (10 mL) was added ethylene oxide (2.5 equiv). The reaction mixture was allowed to warm to rt, continuing stirring overnight. Water (50 mL) was added to the reaction mixture and neutralized with anhydrous Na_2CO_3, and then extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residual oil was purified by flash chromatography on silica gel (DCM:MeOH = 50:1) to give the desired product as colorless oil.

*5.1.5.1. 7-Ethoxy-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5a**).* Yield 77%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.48 (3H, t, J = 7.0 Hz, CH_3), 3.25 (4H, t, J = 5.1 Hz, 2 × $\underline{CH_2}$OH), 3.56 (4H, t, J = 4.9 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 4.14 (2H, q, J = 6.9 Hz, $\underline{CH_2}$OPh), 6.84 (1H, d, J = 1.9 Hz, H-8), 6.96–6.99 (2H, m, H-6, 5′), 7.28 (1H, dd, J = 9.2, 1.5 Hz, H-6′), 7.51 (1H, d, J = 1.9 Hz, H-2′), 7.93 (1H, s, H-2), 8.17 (1H, d, J = 8.9 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.6 (CH_3), 55.7 (OCH_3), 57.3 (2 × CH_2OH), 59.9 (2 × CH_2N), 64.3 (CH_2O), 100.7 (C-8), 111.7 (C-2′), 115.0 (C-6), 118.2 (C-3), 124.4 (C-10), 125.4

(C-1′), 126.05 (C-5′), 126.15 (C-6′), 127.7 (C-5), 138.2 (C-3′), 152.2 (C-2), 155.3 (C-4′), 158.0 (C-9), 163.5 (C-7), 175.8 (C-4).

*5.1.5.2. 7-Propoxy-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5b**).* Yield 76%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.07 (3H, t, J = 7.5 Hz, CH_3), 1.84–1.91 (2H, m, CH_2), 3.25 (4H, t, J = 5.1 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 4.9 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 4.02 (2H, t, J = 6.5 Hz, OCH_2), 6.83 (1H, d, J = 2.0 Hz, H-8), 6.96–6.99 (2H, m, H-6, 5′), 7.28 (1H, dd, J = 8.0, 2.0 Hz, H-6′), 7.51 (1H, d, J = 2.0 Hz, H-2′), 7.93 (1H, s, H-2), 8.17 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.5 (CH_3), 22.4 (CH_2), 55.8 (OCH_3), 57.3 (2 × CH_2OH), 59.9 (2 × CH_2N), 70.2 (CH_2O), 100.6 (C-8), 111.6 (C-2′), 115.1 (C-6), 118.2 (C-3), 124.4 (C-10), 125.3 (C-1′), 126.05 (C-5′), 126.11 (C-6′), 127.6 (C-5), 138.1 (C-3′), 152.3 (C-2), 155.3 (C-4′), 158.0 (C-9), 163.7 (C-7), 175.9 (C-4).

*5.1.5.3. 7-Butoxy-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5c**).* Yield 79%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.00 (3H, t, J = 7.3 Hz, CH_3), 1.49–1.57 (2H, m, γ-CH_2), 1.70–1.86 (2H, m, β-CH_2), 3.25 (4H, t, J = 5.0 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 4.9 Hz, 2 × CH_2N), 3.91 (3H, s, OCH_3), 4.06 (2H, t, J = 6.5 Hz, OCH_2), 6.84 (1H, d, J = 2.1 Hz, H-8), 6.97–6.99 (2H, m, H-6, 5′), 7.28 (1H, dd, J = 6.5, 1.9 Hz, H-6′), 7.51 (1H, d, J = 1.9 Hz, H-2′), 7.93 (1H, s, H-2), 8.17 (1H, d, J = 8.9 Hz, H-5); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 13.8 (CH_3), 19.2 (γ-CH_2), 31.0 (β-CH_2), 55.7 (OCH_3), 57.4 (2 × CH_2OH), 59.9 (2 × CH_2N), 68.5 (CH_2O), 100.7 (C-8), 111.7 (C-2′), 115.0 (C-6), 118.2 (C-3), 124.4 (C-10), 125.4 (C-1′), 126.09 (C-5′), 126.15 (C-6′), 127.7 (C-5), 138.2 (C-3′), 152.2 (C-2), 155.3 (C-4′), 158.0 (C-9), 163.7 (C-7), 175.8 (C-4).

*5.1.5.4. 7-Isopropoxy-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5d**).* Yield 77%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.40 (6H, d, J = 6.0 Hz, 2 × CH_3), 3.25 (4H, t, J = 5.1 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 4.9 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 4.63–4.69 (1H, m, OCH), 6.83 (1H, d, J = 2.2 Hz, H-8), 6.95–6.98 (2H, m, H-6, 5′), 7.28 (1H, dd, J = 6.3, 2.1 Hz, H-6′), 7.51 (1H, d, J = 2.5 Hz, H-2′), 7.92 (1H, s, H-2), 8.17 (1H, d, J = 8.9 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.8 (2 × CH_3), 54.7 (OCH_3), 56.3 (2 × CH_2OH), 58.8 (2 × CH_2N), 69.8 (CHO), 100.6 (C-8), 110.6 (C-2′), 114.6 (C-6), 117.0 (C-3), 123.2 (C-10), 124.4 (C-1′), 125.06 (C-5′), 125.11 (C-6′), 126.7 (C-5), 137.0 (C-3′), 151.2 (C-2), 154.2 (C-4′), 157.0 (C-9), 161.5 (C-7), 174.8 (C-4).

*5.1.5.5. 7-sec-Butoxy-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5e**).* Yield 79%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.01 (3H, t, J = 7.0 Hz, β-CH_3), 1.36 (3H, d, J = 6.0 Hz, α-CH_3), 1.69–1.74 (2H, m, CH_2), 3.25 (4H, t, J = 5.0 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 5.0 Hz, 2 × CH_2N), 3.89 (3H, s, OCH_3), 4.40–4.47 (H, m, OCH), 6.83 (1H, d, J = 1.5 Hz, H-8), 6.95–6.98 (2H, m, H-6, 5′), 7.27 (1H, dd, J = 6.3, 2.1 Hz, H-6′), 7.51 (1H, d, J = 2.5 Hz, H-2′), 7.93 (1H, s, H-2), 8.16 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.7 (β-CH_3), 19.0 (α-CH_3), 29.0 (CH_2), 55.7 (OCH_3), 57.2 (2 × CH_2OH), 59.8 (2 × CH_2N), 75.8 (CHO), 101.6 (C-8), 111.6 (C-2′), 115.6 (C-6), 117.9 (C-3), 124.2 (C-10), 125.3 (C-1′), 125.94 (C-5′), 126.01 (C-6′), 127.7 (C-5), 138.1 (C-3′), 152.2 (C-2), 155.2 (C-4′), 158.0 (C-9), 162.9 (C-7), 175.8 (C-4).

*5.1.5.6. 7-(Pentan-2-yloxy)-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5f**).* Yield 80%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (6H, d, J = 6.5 Hz, 2 × CH_3), 1.73 (2H, q, J = 6.5 Hz, CH_2), 1.84–1.89 (1H, m, CH), 3.25 (4H, t, J = 5.5 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 5.0 Hz, 2 × CH_2N), 3.91 (3H, s, OCH_3), 4.09 (2H, t, J = 6.5 Hz, OCH_2), 6.84 (1H, d, J = 2.0 Hz, H-8), 6.96–7.00 (2H, m, H-6, 5′), 7.28 (1H, dd, J = 6.0, 2.5 Hz, H-6′), 7.51 (1H, d, J = 2.0 Hz, H-2′), 7.93 (1H, s, H-2), 8.17 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.5 (2 × CH_3), 25.0 (CH), 37.6 (CH_2), 55.8 (OCH_3), 57.3 (2 × CH_2OH), 59.9 (2 × CH_2N), 67.1 (CH_2O), 100.6 (C-8), 111.6 (C-2′), 115.1 (C-6), 118.1 (C-3), 124.4 (C-10), 125.4 (C-1′), 126.09 (C-5′), 126.13 (C-6′), 127.6 (C-5), 138.1 (C-3′), 152.2 (C-2), 155.3 (C-4′), 158.0 (C-9), 163.6 (C-7), 175.8 (C-4).

*5.1.5.7. 7-Allyloxy-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5g**).* Yield 73%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.25 (4H, t, J = 5.5 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 5.5 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 4.64 (2H, t, J = 5.0 Hz, OCH_2), 5.36 (1H, dd, J = 9.5, 1.0 Hz, $\underline{CH_2}$=CH), 5.47 (1H, dd, J = 16.0, 1.5 Hz, $\underline{CH_2}$=CH), 6.03–6.10 (1H, m, CH), 6.86 (1H, d, J = 2.0 Hz, H-8), 6.97 (1H, d, J = 8.5 Hz, H-5′), 7.02 (H, dd, J = 6.5, 2.5 Hz, H-6), 7.28 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.51 (1H, d, J = 2.0 Hz, H-2′), 7.93 (1H, s, H-2), 8.19 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 54.7 (OCH_3), 56.3 (2 × CH_2OH), 58.8 (2 × CH_2N), 68.3 (CH_2O), 100.0 (C-8), 110.6 (C-2′), 114.1 (C-6), 117.4 (C-3), 117.6 (CH), 123.4 (C-10), 124.2 (C-1′), 125.05 (C-5′), 125.10 (C-6′), 126.7 (C-5), 131.0 ($\underline{CH_2}$=CH), 137.0 (C-3′), 151.2 (C-2), 154.3 (C-4′), 156.8 (C-9), 162.0 (C-7), 174.8 (C-4).

*5.1.5.8. 7-(2-Methylallyloxy)-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5h**).* Yield 75%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.86 (3H, s, CH_3), 3.25 (4H, t, J = 5.5 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 5.0 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 4.54 (2H, s, OCH_2), 5.05 (1H, s, $\underline{CH_2}$=C), 5.13 (1H, s, $\underline{CH_2}$=C), 6.86 (1H, d, J = 2.0 Hz, H-8), 6.96 (1H, d, J = 8.5 Hz, H-5′), 7.02 (H, dd, J = 6.5, 2.0 Hz, H-6), 7.27 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.50 (1H, d, J = 2.0 Hz, H-2′), 7.93 (1H, s, H-2), 8.18 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.3 (CH_3), 55.7 (OCH_3), 57.2 (2 × CH_2OH), 59.9 (2 × CH_2N), 72.2 (CH_2O), 101.1 (C-8), 111.6 (C-2′), 113.5 ($\underline{CH_2}$=C), 115.1 (C-6), 118.4 (C-3), 124.6 (C-10), 125.2 (C-1′), 125.99 (C-5′), 126.09 (C-6′), 127.7 (C-5), 138.0 (C-3′), 139.8 (CH_2=$\underline{C}$), 152.3 (C-2), 155.3 (C-4′), 157.9 (C-9), 163.2 (C-7), 175.9 (C-4).

*5.1.5.9. 7-(3-Methylbut-2-enyloxy)-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5i**).* Yield 70%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.79 (3H, s, CH_3), 1.83 (3H, s, CH_3), 3.25 (4H, t, J = 5.0 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 5.0 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 4.61 (2H, d, J = 7.0 Hz, OCH_2), 5.50 (1H, t, J = 6.5 Hz, $\underline{CH}$=C), 6.86 (1H, d, J = 2.5 Hz, H-8), 6.97 (1H, d, J = 8.5 Hz, H-5′), 7.00 (H, dd, J = 6.5, 2.5 Hz, H-6), 7.28 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.51 (1H, d, J = 1.5 Hz, H-2′), 7.93 (1H, s, H-2), 8.17 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.3 (CH_3), 25.8 (CH_3), 55.8 (OCH_3), 57.3 (2 × CH_2OH), 59.9 (2 × CH_2N), 65.6 (CH_2O), 101.0 (C-8), 111.7 (C-2′), 115.2 (C-6), 118.3 (C-3), 118.6 ($\underline{CH}$=C), 124.5 (C-10), 125.4 (C-1′), 126.12 (C-5′), 126.17 (C-6′), 127.7 (C-5), 138.1 (C-3′), 139.4 (CH=$\underline{C}$), 152.2 (C-2), 155.3 (C-4′), 158.0 (C-9), 163.4 (C-7), 175.9 (C-4).

*5.1.5.10. 7-(Benzyloxy)-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5j**).* Yield 79%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.25 (4H, t, J = 5.1 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 5.2 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 5.17 (2H, s, OCH_2), 6.93 (1H, d, J = 2.2 Hz, H-8), 6.96 (1H, d, J = 8.5 Hz, H-5′), 7.01 (H, dd, J = 6.6, 2.3 Hz, H-6), 7.27 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.36–7.46 (5H, m, 5 × Ph-H), 7.50 (1H, d, J = 2.5 Hz, H-2′), 7.92 (1H, s, H-2), 8.20 (1H, d, J = 8.9 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.7 (OCH_3), 57.2 (2 × CH_2OH), 59.8 (2 × CH_2N), 70.5 (CH_2O), 101.2 (C-8), 111.6 (C-2′), 115.2 (C-6), 118.5 (C-3), 124.4 (C-10), 125.2 (C-1′), 126.00 (C-5′), 126.05 (C-6′), 127.5 (2 × A_2-C), 127.7 (C-5), 128.4 (A_4-C), 128.8 (2 × A_3-C), 135.6 (A_1-C), 138.1 (C-3′), 152.2 (C-2), 155.3 (C-4′), 157.8 (C-9), 163.1 (C-7), 175.8 (C-4).

*5.1.5.11. 7-Phenethoxy-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5k**).* Yield 82%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.15(2H, t, J = 7.0 Hz, CH_2Ph), 3.25 (4H, t, J = 5.0 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 5.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 4.26 (2H, t, J = 7.0 Hz, OCH_2), 6.83 (1H, d, J = 2.5 Hz, H-8), 6.95 (1H, d, J = 8.5 Hz, H-5′), 6.98 (H, dd, J = 7.0, 2.0 Hz, H-6), 7.26 (1H, dd,

J = 6.0, 1.5 Hz, H-6′), 7.27–7.35(5H, m, 5 × Ph-H), 7.49 (1H, d, J = 2.5 Hz, H-2′), 7.92 (1H, s, H-2), 8.16 (1H, d, J = 8.9 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.5 (CH_2), 55.7 (OCH_3), 57.1 (2 × CH_2OH), 59.9 (2 × CH_2N), 69.3 (CH_2O), 100.7 (C-8), 111.6 (C-2′), 115.0 (C-6), 118.3 (C-3), 124.4 (C-10), 125.2 (C-1′), 125.97 (C-5′), 126.02 (C-6′), 126.8 (A_4-C), 127.7 (C-5), 128.6 (2 × A_2-C), 129.0 (2 × A_3-C), 137.6 (A_1-C), 138.0 (C-3′), 152.3 (C-2), 155.2 (C-4′), 157.9 (C-9), 163.3 (C-7), 175.8 (C-4).

*5.1.5.12. 7-(4-Methylbenzyloxy)-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5l**).* Yield 79%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.39 (3H, s, CH_3), 3.25 (4H, t, J = 5.0 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 5.0 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 5.14 (2H, s, OCH_2), 6.90 (1H, d, J = 2.5 Hz, H-8), 6.96 (1H, d, J = 8.5 Hz, H-5′), 7.01 (H, dd, J = 6.5, 2.5 Hz, H-6), 7.22 (2H, d, J = 8.0 Hz, 2 × A_3-H), 7.27 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.34 (2H, d, J = 7.5 Hz, 2 × A_2-H), 7.51 (1H, d, J = 2.5 Hz, H-2′), 7.91 (1H, s, H-2), 8.20 (1H, d, J = 8.9 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.2 (CH_3), 55.6 (OCH_3), 57.2 (2 × CH_2OH), 59.9 (2 × CH_2N), 70.6 (CH_2O), 101.2 (C-8), 111.6 (C-2′), 115.1 (C-6), 118.5 (C-3), 124.6 (C-10), 125.0 (C-1′), 126.01 (C-5′), 126.07 (C-6′), 127.8 (2 × A_2-C), 127.9 (C-5), 129.5 (2 × A_3-C), 132.5 (A_4-C), 136.7 (A_1-C), 138.2 (C-3′), 152.2 (C-2), 155.1 (C-4′), 157.8 (C-9), 163.1 (C-7), 175.8 (C-4).

*5.1.5.13. 7-Cyclopentyloxy-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5m**).* Yield 78%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.66–2.07 (8H, m, 4 × CH_2), 3.25 (4H, t, J = 5.5 Hz, 2 × $\underline{CH_2}OH$), 3.56 (4H, t, J = 5.5 Hz, 2 × CH_2N), 3.87 (3H, s, OCH_3), 4.83–4.86 (1H, m, CH), 6.81 (1H, d, J = 2.0 Hz, H-8), 6.92–6.95 (2H, m, H-6, 5′), 7.25 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.48 (1H, d, J = 2.5 Hz, H-2′), 7.92 (1H, s, H-2), 8.14 (1H, d, J = 8.9 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.0 (2 × CH_2), 32.7 (2 × CH_2), 55.6 (OCH_3), 56.9 (2 × CH_2OH), 59.8 (2 × CH_2N), 80.2 (CHO), 101.5 (C-8), 111.6 (C-2′), 115.7 (C-6), 117.8 (C-3), 124.3 (C-10), 125.1 (C-1′), 125.70 (C-5′), 125.85 (C-6′), 127.5 (C-5), 138.1 (C-3′), 152.2 (C-2), 155.0 (C-4′), 157.8 (C-9), 162.7 (C-7), 175.8 (C-4).

*5.1.5.14. 7-Cyclohexyloxy-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5n**).* Yield 79%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.35–2.09 (10H, m, 5 × CH_2), 3.25 (4H, t, J = 5.0 Hz, 2 × $\underline{CH_2}OH$), 3.57 (4H, t, J = 5.5 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 4.37–4.40 (1H, m, CH), 6.84 (1H, d, J = 2.5 Hz, H-8), 6.96–6.80 (2H, m, H-6,5′), 7.27 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.51 (1H, d, J = 1.0 Hz, H-2′), 7.92 (1H, s, H-2), 8.16 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.6 (2 × CH_2), 25.5 (CH_2), 31.5 (2 × CH_2), 55.7 (OCH_3), 57.3 (2 × CH_2OH), 59.9 (2 × CH_2N), 76.1 (CH), 101.8 (C-8), 111.6 (C-2′), 115.7 (C-6), 118.0 (C-3), 124.3 (C-10), 125.3 (C-1′), 126.02 (C-5′), 126.11 (C-6′), 127.7 (C-5), 138.1 (C-3′), 152.2 (C-2), 155.2 (C-4′), 158.0 (C-9), 162.5 (C-7), 175.8 (C-4).

*5.1.5.15. 7-Cycloheptyloxy-3-(3-(bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**5o**).* Yield 77%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.51–2.09 (12H, m, 6 × CH_2), 3.25 (4H, t, J = 5.0 Hz, 2 × $\underline{CH_2}OH$), 3.57 (4H, t, J = 5.5 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 4.52–4.55 (1H, m, CH), 6.79 (1H, d, J = 2.0 Hz, H-8), 6.94 (1H, dd, J = 7.0, 2.0 Hz, H-6), 6.96 (1H, d, J = 8.5 Hz, H-5′), 7.27 (1H, dd, J = 6.5, 2.0 Hz, H-6′), 7.51 (1H, d, J = 1.5 Hz, H-2′), 7.91 (1H, s, H-2), 8.16 (1H, d, J = 9.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.9 (2 × CH_2), 28.3 (2 × CH_2), 33.5 (2 × CH_2), 55.7 (OCH_3), 57.3 (2 × CH_2OH), 59.9 (2 × CH_2N), 78.7 (CH), 101.7 (C-8), 111.6 (C-2′), 115.8 (C-6), 117.9 (C-3), 124.3 (C-10), 125.4 (C-1′), 126.04 (C-5′), 126.10 (C-6′), 127.7 (C-5), 138.1 (C-3′), 152.2 (C-2), 155.3 (C-4′), 158.0 (C-9), 162.5 (C-7), 175.8 (C-4).

*5.1.6. General procedure for preparation of **6a**–**6o***

A mixture of compounds **5a**–**5o** (100 mg), $SOCl_2$ (2.5 equiv) and DCM (10 mL) was refluxed for 1.5 h. Water (30 mL) was added into the reaction mixture and extracted with DCM (3 × 30 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residual solid was purified by flash chromatography on silica gel (EtOAc:petroleum ether = 1:10) to give **6a**–**6o** as white powder.

*5.1.6.1. 7-Ethoxy-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6a**).* Yield 72%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.48 (3H, t, J = 6.9 Hz, CH_3), 3.53 (4H, t, J = 5.1 Hz, 2 × CH_2Cl), 3.57 (4H, t, J = 5.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 4.14 (2H, q, J = 6.9 Hz, CH_2), 6.83 (1H, d, J = 2.2 Hz, 8-H), 6.93 (1H, d, J = 8.3 Hz, 5′-H), 6.99 (1H, dd, J = 6.4, 2.3 Hz, 6-H), 7.24 (1H, d, J = 2.1 Hz, 2′-H), 7.27 (1H, dd, J = 7.9, 2.0 Hz, 6′-H), 7.91 (1H, s, 2-H), 8.19 (1H, d, J = 8.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.6 (CH_3), 41.3 (2 × CH_2N), 55.8 (2 × CH_2Cl), 55.8 (OCH_3), 62.5 (CH_2O), 101.6 (C-8), 112.4 (C-2′), 115.6 (C-6), 118.1 (C-3), 124.2 (C-10), 124.5 (C-5′), 124.9 (C-6′), 127.7 (C-5), 137.0 (C-3′), 152.2 (C-2), 154.1 (C-4′), 158.0 (C-9), 162.5 (C-7), 175.7 (C-4); IR (KBr) (cm^{-1}): ν3076, 2928, 2849, 1728, 1630, 1600, 1470, 1412, 1302, 1243, 1172, 1134, 1012, 839, 729, 679; FAB-MS: m/z 436 $[M]^+$, 438 $[M + 2]^+$.

*5.1.6.2. 7-Propoxy-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6b**).* Yield 69%; ^{1}H NMR ($CDCl_3$): δ 1.07 (3H, t, J = 7.5 Hz, CH_3), 1.85–1.89 (2H, m, CH_2), 3.52 (4H, t, J = 5.5 Hz, 2 × CH_2Cl), 3.58 (4H, t, J = 6.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 4.02 (2H, t, J = 6.5 Hz, CH_2O), 6.84 (1H, d, J = 2.0 Hz, 8-H), 6.94 (1H, d, J = 8.5 Hz, 5′-H), 6.98 (1H, dd, J = 6.5, 2.5 Hz, 6-H), 7.24 (1H, s, 2′-H), 7.27 (1H, d, J = 9.5 Hz, 6′-H), 7.92 (1H, s, 2-H), 8.19 (1H, d, J = 8.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.5 (CH_3), 22.4 (CH_2), 40.8 (2 × CH_2N), 55.9 (2 × CH_2Cl), 55.9 (OCH_3), 70.2 (CH_2O), 101.7 (C-8), 112.5 (C-2′), 115.7 (C-6), 118.1 (C-3), 124.5 (C-10), 125.0 (C-5′), 125.2 (C-6′), 127.8 (C-5), 136.8 (C-3′), 152.4 (C-2), 154.0 (C-4′), 158.1 (C-9), 162.9 (C-7), 175.7 (C-4); IR (KBr) (cm^{-1}): ν3078, 2962, 2877, 1738, 1626, 1566, 1508, 1442, 1258, 1201, 1094, 955, 840, 802, 778, 652; FAB-MS: m/z 450 $[M]^+$, 452 $[M + 2]^+$.

*5.1.6.3. 7-Butoxy-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6c**).* Yield 73%; ^{1}H NMR ($CDCl_3$): δ 1.00 (3H, t, J = 7.4 Hz, CH_3), 1.50–1.55 (2H, m, β-CH_2), 1.80–1.85 (2H, m, γ-CH_2), 3.53 (4H, t, J = 6.0 Hz, 2 × CH_2Cl), 3.56 (4H, t, J = 6.0 Hz, 2 × CH_2N), 3.87 (3H, s, OCH_3), 4.06 (2H, t, J = 6.5 Hz, CH_2O), 6.84 (1H, d, J = 2.1 Hz, 8-H), 6.94 (1H, d, J = 8.3 Hz, 5′-H), 6.98 (1H, dd, J = 6.4, 2.3 Hz, 6-H), 7.24 (1H, d, J = 2.1 Hz, 2′-H), 7.27 (1H, dd, J = 7.9, 2.0 Hz, 6′-H), 7.92 (1H, s, 2-H), 8.19 (1H, d, J = 8.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.8 (CH_3), 19.2 (γ-CH_2), 31.9 (β-CH_2), 41.9 (2 × CH_2N), 55.6 (2 × CH_2Cl), 55.7 (OCH_3), 68.2 (CH_2O), 100.6 (C-8), 112.2 (C-2′), 114.9 (C-6), 118.2 (C-3), 124.5 (C-10,1′), 124.6 (C-5′), 124.9 (C-6′), 127.6 (C-5), 136.8 (C-3′), 152.1 (C-2), 154.3 (C-4′), 157.9 (C-9), 163.6 (C-7), 175.8 (C-4); IR (KBr) (cm^{-1}): ν3079, 2960, 2880, 1730, 1625, 1600, 1470, 1381, 1340, 1242, 1161, 1030, 918, 778, 679; FAB-MS: m/z 464 $[M]^+$, 466 $[M + 2]^+$.

*5.1.6.4. 7-Isopropoxy-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6d**).* Yield 70%; ^{1}H NMR ($CDCl_3$): δ 1.41 (6H, d, J = 6.0 Hz, 2 × CH_3), 3.52 (4H, t, J = 5.1 Hz, 2 × CH_2Cl), 3.58 (4H, t, J = 5.0 Hz, 2 × CH_2N), 3.90 (3H, s, OCH_3), 4.65–4.70 (1H, m, CH), 6.83 (1H, d, J = 2.2 Hz, 8-H), 6.94 (1H, d, J = 8.3 Hz, 5′-H), 6.95 (1H, dd, J = 6.4, 2.3 Hz, 6-H), 7.24 (1H, d, J = 2.1 Hz, 2′-H), 7.27 (1H, dd, J = 7.9, 2.0 Hz, 6′-H), 7.91 (1H, s, 2-H), 8.18 (1H, d, J = 8.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.8 (2 × CH_3), 41.9 (2 × CH_2N), 55.7 (2 × CH_2Cl), 55.7 (OCH_3), 70.8 (CHO), 101.6 (C-8), 112.3 (C-2′), 115.5 (C-6), 118.1 (C-3), 124.5 (C-10,1′), 124.7 (C-5′), 125.0 (C-6′),

127.8 (C-5), 136.9 (C-3′), 152.1 (C-2), 154.3 (C-4′), 158.0 (C-9), 162.5 (C-7), 175.8 (C-4); IR (KBr) (cm^{-1}): ν3080, 2965, 2852, 1723, 1638, 1599, 1508, 1466, 1416, 1366, 1293, 1255, 1172, 1093, 975, 916, 802, 718, 652; FAB-MS: *m*/*z* 450 $[M]^+$, 452 $[M + 2]^+$.

*5.1.6.5. 7-sec-Butoxy-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6e**).* Yield 69%; ^1H NMR ($CDCl_3$): δ 1.02 (3H, t, *J* = 7.0 Hz, γ-CH_3), 1.36 (3H, d, *J* = 6.0 Hz, α-CH_3), 1.79 (2H, m, CH_2), 3.53 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.58 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 4.41–4.45 (1H, m, CH), 6.84 (1H, d, *J* = 2.0 Hz, 8-H), 6.94 (1H, d, *J* = 8.3 Hz, 5′-H), 6.97 (1H, dd, *J* = 6.4, 2.5 Hz, 6-H), 7.24 (1H, d, *J* = 2.1 Hz, 2′-H), 7.27 (1H, dd, *J* = 7.9, 2.0 Hz, 6′-H), 7.92 (1H, s, 2-H), 8.18 (1H, d, *J* = 8.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.4 (β-CH_3), 22.4 (α-CH_3), 29.7 (CH_2), 41.1 (2 × CH_2N), 55.8 (2 × CH_2Cl), 55.8 (OCH_3), 75.8 (CHO), 100.7 (C-8), 112.5 (C-2′), 114.8 (C-6), 118.2 (C-3), 124.5 (C-10,1′), 124.6 (C-5′), 124.9 (C-6′), 127.7 (C-5), 136.8 (C-3′), 152.3 (C-2), 154.1 (C-4′), 158.0 (C-9), 163.7 (C-7), 175.8 (C-4); IR (KBr) (cm^{-1}): ν3075, 2959, 2853, 1731, 1625, 1566, 1438, 1323, 1258, 1200, 1094, 1008, 955, 838, 722; FAB-MS: *m*/*z* 464 $[M]^+$, 466 $[M + 2]^+$.

*5.1.6.6. 7-(Pentan-2-yloxy)-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6f**).* Yield 72%; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.98 (6H, d, *J* = 6.5 Hz, 2 × CH_3), 1.72–1.76 (2H, m, CH_2), 1.84–1.88 (1H, m, CH), 3.51 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.58 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.87 (3H, s, OCH_3), 4.08 (2H, t, *J* = 6.5 Hz, CH_2), 6.84 (1H, d, *J* = 2.0 Hz, 8-H), 6.93 (1H, d, *J* = 8.5 Hz, 5′-H), 6.98 (1H, dd, *J* = 6.5, 2.5 Hz, 6-H), 7.23 (1H, d, *J* = 2.1 Hz, 2′-H), 7.27 (1H, dd, *J* = 7.9, 2.0 Hz, 6′-H), 7.91 (1H, s, 2-H), 8.18 (1H, d, *J* = 9.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.5 (2 × CH_3), 25.0 (CH), 37.6 (CH_2), 41.9 (2 × CH_2N), 55.6 (2 × CH_2Cl), 55.7 (OCH_3), 67.1 (CH_2O), 100.6 (C-8), 112.2 (C-2′), 114.9 (C-6), 118.2 (C-3), 124.5 (C-10,1′), 124.6 (C-5′), 124.9 (C-6′), 127.6 (C-5), 136.8 (C-3′), 152.1 (C-2), 154.3 (C-4′), 157.9 (C-9), 163.6 (C-7), 175.8 (C-4); IR (KBr) (cm^{-1}): ν3077, 2955, 2852, 1730, 1625, 1507, 1439, 1366, 1258, 1199, 1029, 959, 802, 729; FAB-MS: *m*/*z* 478 $[M]^+$, 480 $[M + 2]^+$.

*5.1.6.7. 7-Allyloxy-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6g**).* Yield 71%; ^1H NMR ($CDCl_3$): δ 3.53 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.58 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 4.65 (2H, d, *J* = 5.0 Hz, CH_2), 5.37 (1H, d, *J* = 9.5 Hz, $\underline{CH_2}$=CH), 5.47 (1H, d, *J* = 17.0 Hz, $\underline{CH_2}$=CH), 6.04–6.10 (1H, m, CH), 6.87 (1H, d, *J* = 2.0 Hz, 8-H), 6.94 (1H, d, *J* = 7.5 Hz, 5′-H), 7.01 (1H, dd, *J* = 7.0, 2.0 Hz, 6-H), 7.23 (1H, d, *J* = 2.0 Hz, 2′-H), 7.27 (1H, dd, *J* = 6.5, 2.5 Hz, 6′-H), 7.92 (1H, s, 2-H), 8.20 (1H, d, *J* = 9.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 41.9 (2 × CH_2N), 55.6 (2 × CH_2Cl), 55.7 (OCH_3), 69.3 (CH_2O), 101.1 (C-8), 112.2 (C-2′), 114.9 (C-6), 118.5 (C-3), 118.5 (CH), 124.5 (C-10,1′), 124.6 (C-5′), 124.9 (C-6′), 127.8 (C-5), 132.1 ($\underline{CH_2}$=CH), 136.8 (C-3′), 152.2 (C-2), 154.3 (C-4′), 157.8 (C-9), 162.9 (C-7), 175.8 (C-4); IR (KBr) (cm^{-1}): ν3100, 3077, 2982, 2924, 2859, 1734, 1634, 1569, 1466, 1417, 1305, 1254, 1199, 1094, 914, 863, 803, 776, 716; FAB-MS: *m*/*z* 448 $[M]^+$, 450 $[M + 2]^+$.

*5.1.6.8. 7-(2-Methylallyloxy)-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6h**).* Yield 73%; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.86 (3H, s, CH_3), 3.51 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.57 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 4.54 (2H, s, OCH_2), 5.05 (1H, s, $\underline{CH_2}$=C), 5.13 (1H, s, $\underline{CH_2}$=C), 6.87 (1H, d, *J* = 2.0 Hz, 8-H), 6.93 (1H, d, *J* = 8.0 Hz, 5′-H), 7.02 (1H, dd, *J* = 6.0, 2.0 Hz, 6-H), 7.23 (1H, d, *J* = 2.0 Hz, 2′-H), 7.27 (1H, dd, *J* = 6.0, 2.0 Hz, 6′-H), 7.92 (1H, s, 2-H), 8.20 (1H, d, *J* = 9.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.3 (CH_3), 41.9 (2 × CH_2N), 55.6 (2 × CH_2Cl), 55.7 (OCH_3), 72.2 (CH_2O), 101.1 (C-8), 112.2 (C-2′), 113.6 ($\underline{CH_2}$=C), 115.03 (C-6), 118.5 (C-3), 124.6 (C-10,1′), 124.9 (C-5′), 125.0 (C-6′), 127.7 (C-5), 136.8 (C-3′), 152.2 (C-2), 154.3 (C-4′), 157.8 (C-9), 163.1 (C-7), 175.8 (C-4). IR (KBr) (cm^{-1}): ν3091, 3077, 2969, 2833, 1728, 1626, 1569, 1442, 1305, 1254, 1140, 1028, 975, 863, 803, 716; FAB-MS: *m*/*z* 462 $[M]^+$, 464 $[M + 2]^+$.

*5.1.6.9. 7-(3-Methylbut-2-enyloxy)-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6i**).* Yield 74%; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.86 (3H, s, CH_3), 3.52 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.57 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 4.55 (2H, s, OCH_2), 5.09 (2H, s, CH_2), 6.86 (1H, d, *J* = 2.0 Hz, 8-H), 6.94 (1H, d, *J* = 8.5 Hz, 5′-H), 7.01 (1H, dd, *J* = 7.0, 2.0 Hz, 6-H), 7.24 (1H, s, 2′-H), 7.26 (1H, d, *J* = 8.0 Hz, 6′-H), 7.91 (1H, s, 2-H), 8.20 (1H, d, *J* = 9.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.3 (CH_3), 25.8 (CH_3), 41.9 (2 × CH_2N), 55.6 (2 × CH_2Cl), 55.7 (OCH_3), 65.5 (CH_2O), 100.9 (C-8), 112.2 (C-2′), 115.1 (C-6), 118.3 (C-3), 118.6 ($\underline{CH}$=C), 124.6 (C-10,1′), 124.6 (C-5′), 125.0 (C-6′), 127.7 (C-5), 136.8 (C-3′), 139.4 (CH=$\underline{C}$), 152.1 (C-2), 154.3 (C-4′), 157.9 (C-9), 163.3 (C-7), 175.8 (C-4); IR (KBr) (cm^{-1}): ν3097, 3078, 2947, 2814, 1734, 1636, 1569, 1445, 1316, 1274, 1202, 1139, 1024, 968, 864, 806, 750; FAB-MS: *m*/*z* 476 $[M]^+$, 478 $[M + 2]^+$.

*5.1.6.10. 7-(Benzyloxy)-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6j**).* Yield 70%; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.53 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.58 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 5.12 (2H, s, CH_2), 6.93 (1H, d, *J* = 2.0 Hz, 8-H), 7.01 (1H, d, *J* = 8.5 Hz, 5′-H), 7.08 (1H, dd, *J* = 7.0, 2.0 Hz, 6-H), 7.24 (1H, d, *J* = 2.5 Hz, 2′-H), 7.26 (1H, d, *J* = 8.0, 2.5 Hz, 6′-H), 7.35–7.46 (5H, m, 5 × Ar-H), 7.92 (1H, s, 2-H), 8.20 (1H, d, *J* = 9.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 41.9 (2 × CH_2N), 55.6 (2 × CH_2Cl), 55.7 (OCH_3), 70.5 (CH_2O), 101.3 (C-8), 112.2 (C-2′), 115.1 (C-6), 118.6 (C-3), 124.5 (C-10,1′), 124.6 (C-5′), 125.0 (C-6′), 127.5 (2 × A_2-C), 127.8 (C-5), 128.4 (A_4-C), 128.8 (2 × A_3-C), 135.7 (A_1-C), 136.8 (C-3′), 152.2 (C-2), 154.3 (C-4′), 157.8 (C-9), 163.0 (C-7), 175.8 (C-4); IR (KBr) (cm^{-1}): ν3069, 2957, 2924, 2852, 1729, 1636, 1508, 1442, 1364, 1249, 1199, 1094, 1026, 961, 848, 805, 759; FAB-MS: *m*/*z* 498 $[M]^+$, 500 $[M + 2]^+$.

*5.1.6.11. 7-Phenethoxy-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6k**).* Yield 70%; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.15 (2H, t, *J* = 6.5 Hz, CH_2Ph), 3.53 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.58 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 4.26 (2H, t, *J* = 7.0 Hz, CH_2O), 6.83 (1H, d, *J* = 2.0 Hz, 8-H), 6.94 (1H, d, *J* = 8.5 Hz, 5′-H), 6.98 (1H, dd, *J* = 7.0, 2.0 Hz, 6-H), 7.23 (1H, d, *J* = 2.0 Hz, 2′-H), 7.26 (1H, dd, *J* = 7.0, 2.0 Hz, H-6′), 7.28–7.36 (5H, m, 5 × Ph-H), 7.91 (1H, s, 2-H), 8.19 (1H, d, *J* = 9.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.5 (CH_2), 41.9 (2 × CH_2N), 55.7 (2 × CH_2Cl), 55.7 (OCH_3), 69.3 (CH_2O), 100.8 (C-8), 112.3 (C-2′), 114.9 (C-6), 118.4 (C-3), 124.6 (C-10,1′), 124.7 (C-5′), 125.0 (C-6′), 126.7 (A_4-C), 127.8 (C-5), 128.6 (2 × A_2-C), 129.0 (2 × A_3-C), 136.9 (A_1-C), 137.6 (C-3′), 152.1 (C-2), 154.4 (C-4′), 157.9 (C-9), 163.2 (C-7), 175.8 (C-4); IR (KBr) (cm^{-1}): ν3087, 2967, 2922, 2854, 2814, 1740, 1632, 1596, 1445, 1274, 1201, 1097, 1024, 968, 864, 806, 750; FAB-MS: *m*/*z* 512 $[M]^+$, 514 $[M + 2]^+$.

*5.1.6.12. 7-(4-Methylbenzyloxy)-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6l**).* Yield 75%; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.39 (3H, s, CH_3Ph), 3.53 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.58 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 5.13 (2H, s, CH_2O), 6.92 (1H, d, *J* = 2.0 Hz, 8-H), 6.95 (1H, d, *J* = 8.5 Hz, 5′-H), 7.05 (1H, dd, *J* = 7.0, 2.0 Hz, 6-H), 7.22 (2H, d, *J* = 8.0 Hz, 2 × A_3-H), 7.24 (1H, d, *J* = 2.5 Hz, 2′-H), 7.27 (1H, dd, *J* = 6.5, 2.0 Hz, H-6′), 7.34 (2H, d, *J* = 7.5 Hz, 2 × A_2-H), 7.91 (1H, s, 2-H), 8.20 (1H, d, *J* = 9.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.22 (CH_3), 41.98 (2 × CH_2N), 55.73 (2 × CH_2Cl), 55.76 (OCH_3), 70.59 (CH_2O), 101.33 (C-8), 112.32 (C-2′), 115.13 (C-6), 118.59 (C-3), 124.58 (C-10,1′), 124.80 (C-5′), 125.05 (C-6′), 127.69 (2 × A_2-C), 127.83 (C-5), 129.47 (2 × A_3-C), 132.73 (A_4-C), 136.95 (A_1-C), 138.32 (C-3′), 152.15 (C-2), 154.42 (C-4′), 157.89 (C-9), 163.18 (C-7), 175.80 (C-4); IR (KBr)

(cm^{-1}): ν3075, 2957, 2924, 2855, 2819, 1731, 1624, 1595, 1508, 1440, 1363, 1250, 1197, 1138, 1093, 962, 863, 807, 747; FAB-MS: *m*/*z* 512 $[M]^+$, 514 $[M + 2]^+$.

*5.1.6.13. 7-Cyclopentyloxy-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6m**).* Yield 72%; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.25–2.01 (8H, m, 4 × CH_2), 3.53 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.57 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 4.83–4.86 (1H, m, CH), 6.82 (1H, d, *J* = 2.0 Hz, 8-H), 6.94 (1H, d, *J* = 8.3 Hz, 5′-H), 6.97 (1H, dd, *J* = 6.4, 2.5 Hz, 6-H), 7.24 (1H, d, *J* = 2.0 Hz, 2′-H), 7.27 (1H, d, *J* = 7.5, 2.5 Hz, 6′-H), 7.90 (1H, s, 2-H), 8.17 (1H, d, *J* = 8.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.1 (2 × CH_2), 32.8 (2 × CH_2), 41.9 (2 × CH_2N), 55.7 (2 × CH_2Cl), 55.7 (OCH_3), 80.3 (CH), 101.6 (C-8), 112.3 (C-2′), 115.7 (C-6), 118.0 (C-3), 124.6 (C-10,1′), 124.7 (C-5′), 125.0 (C-6′), 127.7 (C-5), 136.8 (C-3′), 152.1 (C-2), 154.3 (C-4′), 157.9 (C-9), 162.7 (C-7), 175.9 (C-4); IR (KBr) (cm^{-1}): ν3077, 2925, 2855, 1731, 1623, 1597, 1509, 1439, 1363, 1255, 1187, 1139, 1094, 988, 878, 811, 734; FAB-MS: *m*/*z* 476 $[M]^+$, 478 $[M + 2]^+$.

*5.1.6.14. 7-Cyclohexyloxy-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6n**).* Yield 70%; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.30–2.01 (10H, m, 5 × CH_2), 3.53 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.57 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.86 (3H, s, OCH_3), 4.34–4.38 (1H, m, CH), 6.83 (1H, d, *J* = 2.0 Hz, 8-H), 6.94 (1H, d, *J* = 8.3 Hz, 5′-H), 6.97 (1H, dd, *J* = 6.4, 2.5 Hz, 6-H), 7.24 (1H, d, *J* = 2.0 Hz, 2′-H), 7.27 (1H, dd, *J* = 8.0, 2.5 Hz, 6′-H), 7.90 (1H, s, 2-H), 8.17 (1H, d, *J* = 8.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.6 (2 × CH_2), 25.5 (CH_2), 31.5 (2 × CH_2), 41.9 (2 × CH_2N), 55.6 (2 × CH_2Cl), 55.7 (OCH_3), 76.2 (CH), 101.78 (C-8), 112.2 (C-2′), 115.7 (C-6), 118.0 (C-3), 124.5 (C-10,1′), 124.7 (C-5′), 125.0 (C-6′), 127.6 (C-5), 136.8 (C-3′), 152.1 (C-2), 154.3 (C-4′), 158.0 (C-9), 162.5 (C-7), 175.8 (C-4); IR (KBr) (cm^{-1}): ν3078, 2927, 2853, 1738, 1636, 1597, 1509, 1439, 1305, 1255, 1202, 1139, 1019, 988, 836, 781, 734; FAB-MS: *m*/*z* 490 $[M]^+$, 492 $[M + 2]^+$.

*5.1.6.15. 7-Cycloheptyloxy-3-(3-(bis(2-chloroethyl)amino)-4-methoxyphenyl)-4H-chromen-4-one (**6o**).* Yield 66%; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.51–2.01 (12H, m, 6 × CH_2), 3.53 (4H, t, *J* = 6.0 Hz, 2 × CH_2Cl), 3.57 (4H, t, *J* = 6.0 Hz, 2 × CH_2N), 3.88 (3H, s, OCH_3), 4.52–4.55 (1H, m, CH), 6.79 (1H, d, *J* = 2.0 Hz, 8-H), 6.92 (1H, d, *J* = 8.3 Hz, 5′-H), 6.95 (1H, d, *J* = 6.0, 2.5 Hz, 6-H), 7.23 (1H, d, *J* = 2.0 Hz, 2′-H), 7.27 (1H, dd, *J* = 8.0, 2.0 Hz, 6′-H), 7.90 (1H, s, 2-H), 8.18 (1H, d, *J* = 8.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.9 (2 × CH_2), 28.3 (2 × CH_2), 33.5 (2 × CH_2), 41.9 (2 × CH_2N), 55.7 (2 × CH_2Cl), 55.7 (OCH_3), 78.7 (CH), 101.7 (C-8), 112.3 (C-2′), 115.6 (C-6), 118.0 (C-3), 124.5 (C-10, 1′), 124.7 (C-5′), 125.0 (C-6′), 127.7 (C-5), 136.9 (C-3′), 152.0 (C-2), 154.3 (C-4′), 158.0 (C-9), 162.4 (C-7), 175.8 (C-4); IR (KBr) (cm^{-1}): ν3078, 2933, 2860, 1738, 1643, 1609, 1499, 1440, 1293, 1253, 1200, 1137, 1022, 993, 865, 829, 743; FAB-MS: *m*/*z* 504 $[M]^+$, 506 $[M + 2]^+$.

*5.1.7. 3-(3-(Bis(2-hydroxyethyl)amino)-4-methoxyphenyl)-7-hydroxy-4H-chromen-4-one (**7**)*

Compound **5j** (500 mg, 1 mmol) was dissolved in MeOH (10 mL), and 10% Pd/C (50 mg, 10% weight of **5j**) was added, and the mixture was hydrogenated at room temperature and under atmospheric pressure for about 1 h. The reaction mixture was filtered off via a Celite pad, rinsing the filter cake with MeOH (2 × 5 mL). The combined filtrates were evaporated to dryness to afford compound **7** (368 mg; 90%) as white solid. The product was pure enough for next step. ^1H NMR (DMSO-d_6, 500 MHz): δ 3.20 (4H, t, *J* = 8.0 Hz, 2 × $\underline{CH_2}OH$), 3.48 (4H, t, *J* = 7.5 Hz, 2 × CH_2N), 3.80 (3H, s, OCH_3), 6.86 (1H, d, *J* = 2.2 Hz, H-8), 6.92 (1H, d, *J* = 8.5 Hz, H-5′), 6.97 (H, dd, *J* = 6.6, 2.3 Hz, H-6), 7.10 (1H, dd, *J* = 6.5, 2.0 Hz, H-6′), 7.20 (1H, d, *J* = 2.5 Hz, H-2′), 7.97 (1H, d, *J* = 11.0 Hz, H-5), 8.30 (1H, s, H-2); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 55.5 (OCH_3), 57.4 (2 × CH_2OH), 59.1 (2 × CH_2N), 70.5 (CH_2O), 102.1 (C-8), 112.0 (C-2′), 115.2 (C-6), 116.7 (C-3), 121.7 (C-10), 122.5 (C-1′), 123.6 (C-5′), 124.3 (C-6′), 127.3 (C-5), 139.1(C-3′), 152.5 (C-2), 153.1 (C-4′), 157.4 (C-9), 162.6 (C-7), 174.7 (C-4).

*5.1.8. 3-(3-(Bis(2-chloroethyl)amino)-4-methoxyphenyl)-7-hydroxy-4H-chromen-4-one (**8**)*

A mixture of compound **7** (100 mg), $SOCl_2$ (2.5 equiv) and DCM (10 mL) was refluxed for 1.5 h. Water (30 mL) was added into the reaction mixture and extracted with DCM (3 × 30 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residual solid was purified by flash chromatography (EtOAc:petroleum ether = 1:10) to give compound **8** as white powder. Yield 70%; ^1H NMR (DMSO-d_6, 500 MHz): δ 3.50 (4H, t, *J* = 3.5 Hz, 2 × $\underline{CH_2}Cl$), 3.66 (4H, t, *J* = 7.0 Hz, 2 × CH_2N), 3.84 (3H, s, OCH_3), 5.17 (2H, s, OCH_2), 6.88 (1H, d, *J* = 2.2 Hz, H-8), 6.94 (1H, d, *J* = 11.0 Hz, H-5′), 7.03 (H, dd, *J* = 9.0, 2.3 Hz, H-6), 7.20 (1H, dd, *J* = 6.5, 2.0 Hz, H-6′), 7.22 (1H, d, *J* = 2.5 Hz, H-2′), 7.97 (1H, d, *J* = 11.0 Hz, H-5), 8.35 (1H, s, H-2); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 42.5 (2 × CH_2N), 54.8 (2 × CH_2Cl), 56.2 (OCH_3), 102.6 (C-8), 112.9 (C-2′), 115.6 (C-6), 117.1 (C-3), 123.2 (C-10), 123.6(C-1′), 124.2 (C-5′), 124.9 (C-6′), 127.7 (C-5), 137.2 (C-3′), 153.3 (C-2), 153.7 (C-4′), 157.9 (C-9), 163.0 (C-7), 175.1 (C-4); IR (KBr) (cm^{-1}): ν3305, 3069, 2929, 2850, 1625, 1578, 1508, 1455, 1383, 1241, 1217, 1196, 1029, 982, 850, 785, 741; FAB-MS: *m*/*z* 408 $[M]^+$, 410 $[M + 2]^+$.

5.2. Cell line and culture conditions

SH-SY5Y (human neuroblastoma cell line), HCT-116 (human colon cancer cell line), DU-145 (human prostate carcinoma cell line), Hela (human cervical carcinoma cell line) and SGC-7901 (human gastric cell line) were kindly provided by Shanghai Jiao-Tong University. The cell was routinely cultured in RPMI-1640 medium or DMEM, supplemented with 10% neonatal bovine serum (NBS) or 10% fetal bovine serum (FBS). The culture was maintained at 37 °C with a gas mixture of 5% CO_2/95% air. All media were supplement with 100 U/mL penicillin and 100 μg/mL streptomycin.

5.3. Cell viability assay

The cytotoxic activity *in vitro* was measured using the MTT assay. The MTT solution (10.0 μL/well) was added in culture media after cells were treated with various concentrations of compounds for 72 h, and cells were incubated for further 4 h at 37 °C. The purple formazan crystals were dissolved in 100 μL DMSO. After 10 min, the plates were read on an automated microplate spectrophotometer (Bio-Tek Instruments, Winooski, VT) at 570 nm and 630 nm. Assays were performed in triplicate on three independent experiments. The concentration required for 50% inhibition of cell viability (IC_{50}) was calculated using the software "Dose-Effect Analysis with Microcomputers". The tumor cell lines panel consisted of HCT-116, SH-SY5Y, DU-145, Hela, SGC-7901. In all of these experiments, three replicate wells were used to determine each point.

5.4. Cell cycle analysis

The cell cycle was analyzed by flow cytometry. Briefly, cells were treated with different concentrations of compounds **6d** and **6n** for 48 h. After incubation, a total of 1 × 10^8 cells were harvested from the treated and normal samples. The cells were washed twice with PBS and fixed in 75% ice-cold ethanol for at least overnight. The sample was concentrated by removing EtOH and staining the cellular DNA with fluorescent solution (1% (v/v) Triton X-100, 0.01% RNase, 0.05% PI) for 30 min at 4 °C in darkness. The cell cycle distribution was then detected by flow cytometry using a Cell Lab Quanta SC (Beckman Coulter, Fullerton, CA). All experiments were performed three times.

5.5. Annexin V-FITC/PI assay

Cells in different states were observed with an annexin V-FITC/PI double-staining kit by flow cytometry. Cells were treated with different concentrations of compounds **6d** and **6n** for 48 h. After incubation, cells were collected and washed twice in cold PBS and resuspended in 200 μL of binding buffer at 1×10^5 cells/mL. The samples were incubated with 5 μL of Annexin V-FITC and propidium iodide (PI) in the dark for 15 min at room temperature. Finally, samples were analyzed by flow cytometry and evaluated based on the percentage of cells for Annexin V positive. All experiments were performed three times.

Acknowledgments

We thank the financial support from 2010 Industry for Attracting Ph. D. Scientists program of Jiangsu Province (J. Ren) and the Priority Academic Program Development (PAPD) of Jiangsu Higher Education Institutions (X. Chen).

References

[1] V.M. Malikov, M.P. Yuldashev, Chem. Nat. Compd. 38 (2002) 473–519.
[2] M.J. del Bano, J. Lorente, J. Castillo, et al., J. Agric. Food Chem. 52 (2004) 4987–4992.
[3] P.L. Whitten, S. Kudo, K.K. Okubo, CRC Press, Boca Raton, Fla, USA, 1997, pp. 117–137.
[4] G.M. Boland, D.M.X. Donnelly, Nat. Prod. Rep. 15 (1998) 241–260.
[5] X. Yu, W. Wang, M. Yang, Food Chem. 104 (2007) 715–720.
[6] Y. Ungar, O.F. Osundahunsi, E. Shimoni, J. Agric. Food Chem. 51 (2003) 4394–4399.
[7] S. Sato, J. Takeo, C. Aoyama, H. Kawahara, Bioorg. Med. Chem. 15 (2007) 3445–3449.
[8] Z.-N. Ji, W.Y. Zhao, G.R. Liao, et al., Gynecol. Endocrinol. 22 (2006) 578–584.
[9] S. Medjakovic, A. Jungbauer, J. Steroid Biochem. Mol. Biol. 108 (2008) 171–177.
[10] H. Xiang, W. Zhao, H. Xiao, et al., Bioorg. Med. Chem. 18 (2010) 3036–3042.
[11] Y. Yang, W.-J. Mao, H.-Q. Li, et al., Res. Lett. Org. Chem. 2008 (2008) 1–4.
[12] N.I. Baracu, A.T. Balaban, in: D.E. Wilman (Ed.), Chemistry of Antitumor Agents, Blackie, Glasgow, London, 1990, pp. 62–130.
[13] J. Hansson, R. Lewensohn, U. Ringborg, B. Nilsson, Cancer Res. 47 (1987) 2631–2637.
[14] S.R. Rajski, R.M. Williams, Chem. Rev. 98 (1998) 2723–2796.
[15] S.M. Rink, P.B. Hopkins, Bioorg. Med. Chem. Lett. 5 (1995) 2845–2850.
[16] K. Suzukake, B.P. Vistica, D.T. Vistica, Biochem. Pharmacol. 32 (1983) 165–167.
[17] M. Rodney, J.P. Carney, M.R. Kelley, B.J. Glassner, D.A. Williams, L. Samson, Proc. Natl. Acad. Sci. U.S.A. 93 (1996) 206–210.
[18] T. Facon, J.Y. Mary, C. Hulin, et al., Lancet 370 (2007) 1209–1218.
[19] C.J. Springer, I. Niculescu-Duvaz, Anti-Cancer Drug Des. 10 (1995) 361–372.
[20] M.J. O'Connell, N.C. Walworth, A.M. Carr, Trends Cell Biol. 10 (2000) 296–303.