European Journal of Medicinal Chemistry 47 (2012) 530–545

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis and anticancer activity of 4β-alkylamidochalcone and 4β-cinnamido linked podophyllotoxins as apoptotic inducing agents

Ahmed Kamal [a,c,*], Adla Mallareddy [a], Paidakula Suresh [a], V. Lakshma Nayak [b], Rajesh V.C.R.N.C. Shetti [a], N. Sankara Rao [a], Jaki R. Tamboli [a], Thokhir B. Shaik [a], M.V.P.S. Vishnuvardhan [b], S. Ramakrishna [b]

[a] Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 607, India
[b] Pharmacology Division, Indian Institute of Chemical Technology, Hyderabad 500 607, India
[c] Catalytic Chemistry Chair, Chemistry Department, College of Science, King Saud University, Riyadh 11451, Saudi Arabia

ARTICLE INFO

Article history:
Received 23 September 2011
Received in revised form
10 November 2011
Accepted 10 November 2011
Available online 20 November 2011

Keywords:
Apoptosis
Anticancer activity
Caspase-3
Cell cycle analysis
Podophyllotoxin

ABSTRACT

A series of 4β-alkylamidochalcone and 4β-cinnamido linked podophyllotoxin congeners have been synthesized. All the twenty nine compounds were evaluated for anticancer activity against five human cancer cell lines (A-549, A375, MCF-7, HT-29 and ACHN). Some of the synthesized compounds showed good anticancer activity that is comparable to etoposide. The IC_{50} of compounds **17a** and **17f** is 2.7 and 2.1 μM respectively against A-549 cancer cell line. Flow cytometric analysis showed that these two compounds arrested the cell cycle in the G2/M phase leading to caspase-3 dependent apoptotic cell death. Further, Hoechst 33258 staining and DNA fragmentation assay also suggested that **17a** and **17f** induced cell death by apoptosis.

1. Introduction

Podophyllotoxin (**1**) is a well known naturally occurring antitumor lignan lactone isolated from the genus *Podophyllum* [1]. Podophyllotoxin exhibits cytotoxicity by inhibition of tubulin polymerization [2]. The structural modifications of podophyllotoxin resulted in the development of several clinically useful compounds like etoposide (**2**), teniposide (**3**) and the water-soluble prodrug, etopophos (**4**) [3–5]. These compounds have shown to inhibit DNA topoisomerase-II (topo-II) by stabilizing the covalent topo-II DNA complex [6] and are used against a variety of cancers [7–9]. However, their clinical use has encountered certain limitations, such as poor water solubility, development of drug resistance, metabolic inactivation, and certain toxic effects [10]. In order to obtain better therapeutic agents, a great number of podophyllotoxin analogs have been synthesized. This has led to the development of NK-611 (**5**) and GL-331 (**6**) (Fig. 1). The biological studies on these synthesized analogs have provided a better understanding in the knowledge relating to the structure–activity relationships. GL-331 contains a *p*-nitroanilino moiety at the 4-position instead of a glycoside of etoposide, which proved to be more potent than etoposide. GL-331 is also an inhibitor of topo-II and induces apoptotic cell death through independent mechanism which contributes to its cytotoxicity [11]. This compound has underwent phase II clinical trials for the treatment of various cancers [12].

Chalcones represent an important group of natural products [13,14], that received significant attention for their antitumor properties. In addition, chalcones have been reported for a wide range of pharmacological activities including cytotoxicity [15] and anticancer activity [16,17]. Moreover, recent studies have shown that these chalcones induce apoptosis in a variety of cell types [18,19].

In chalcones, particularly methoxy chalcones possess potential anticancer activity. The trimethoxy chalcones synthesized by Ducki and co-workers [20] showed potential anticancer activity by binding strongly to tubulin at a site shared with, or close to, the colchicines binding site [21,22]. The anticancer activity and tubulin binding property of these chalcones are comparable with combretastatin A-4 (CA-4) and prodrugs of these potential chalcones are under pre-clinical evaluation. Further, in this trimethoxy chalcone series different analogues have been synthesized by different groups and evaluated for their cytotoxicity. These compounds have shown promising activity against different cancer cell lines [23]. Substituted cinnamic acids and its derivatives [24] are widely

* Corresponding author. Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 607, India. Tel.: +91 40 27193157; fax: +91 40 27193189.
E-mail address: ahmedkamal@iict.res.in (A. Kamal).

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doi:10.1016/j.ejmech.2011.11.024

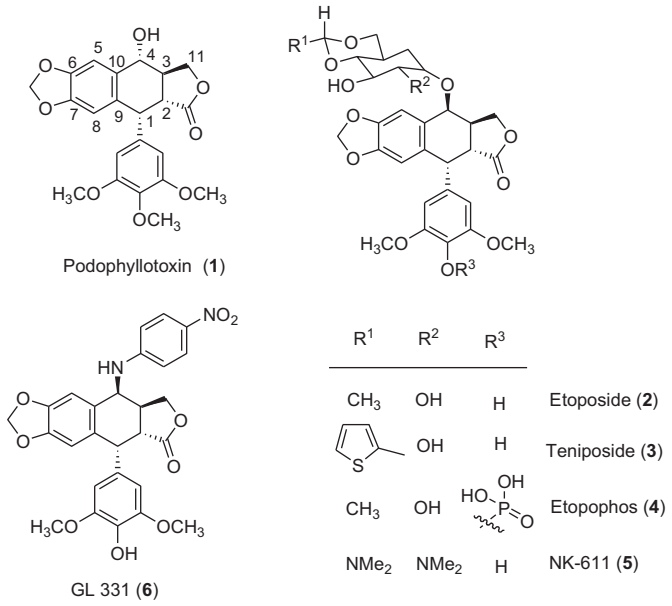


Fig. 1. Structures of podophyllotoxin derivatives.

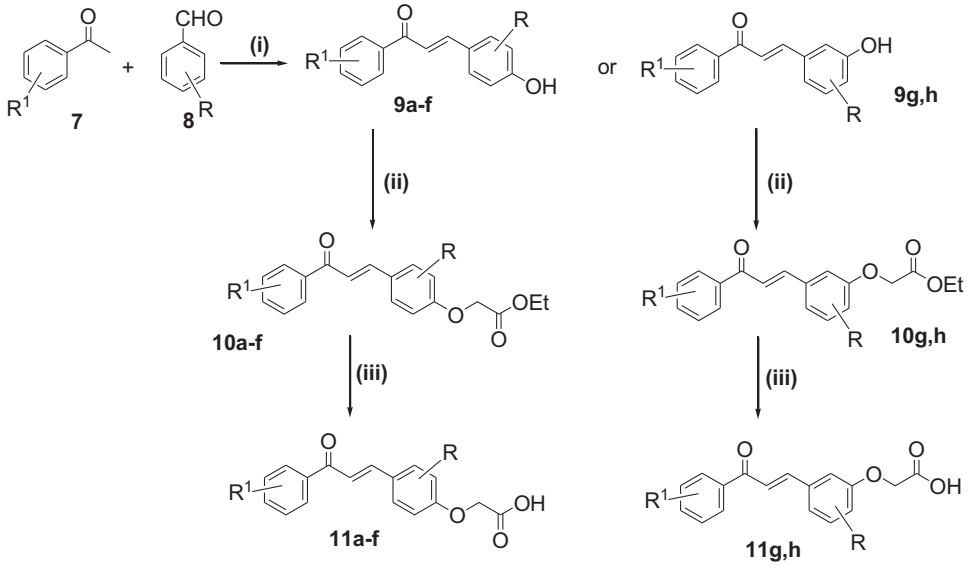
distributed in the plant kingdom and are reported as cellular antioxidants, anti-inflammatory agents, or inhibitors of enzymes involved in cell proliferation, and some biological activities [25–27]. Antitumor activities of various cinnamic acid derivatives were also explored by many research groups. Particularly, cinnamic acid ester derivatives showed the potential antitumor activity [28–30]. Some of methoxy and halo substituted cinnamic acid derivatives showed good anticancer activity [31].

In an ongoing effort we have been involved in the development of new synthetic procedures [32] for the podophyllotoxin-based compounds and also in the design and synthesis of new analogs of podophyllotoxin as potential anticancer agents [33,34]. In continuation of these efforts in search for novel and selective anticancer agents, we synthesized some new conjugates of podophyllotoxin by linking the chalcone and cinnamic acid moieties to the 4β-aminopodophyllotoxin scaffold through stable alkane spacers and amide bond formation. These compounds were evaluated for their anticancer activity and based on the promising activity obtained it was considered of interest to investigate their role in the cell proliferation and apoptosis by using human lung cancer cell line A-549.

2. Results and discussion

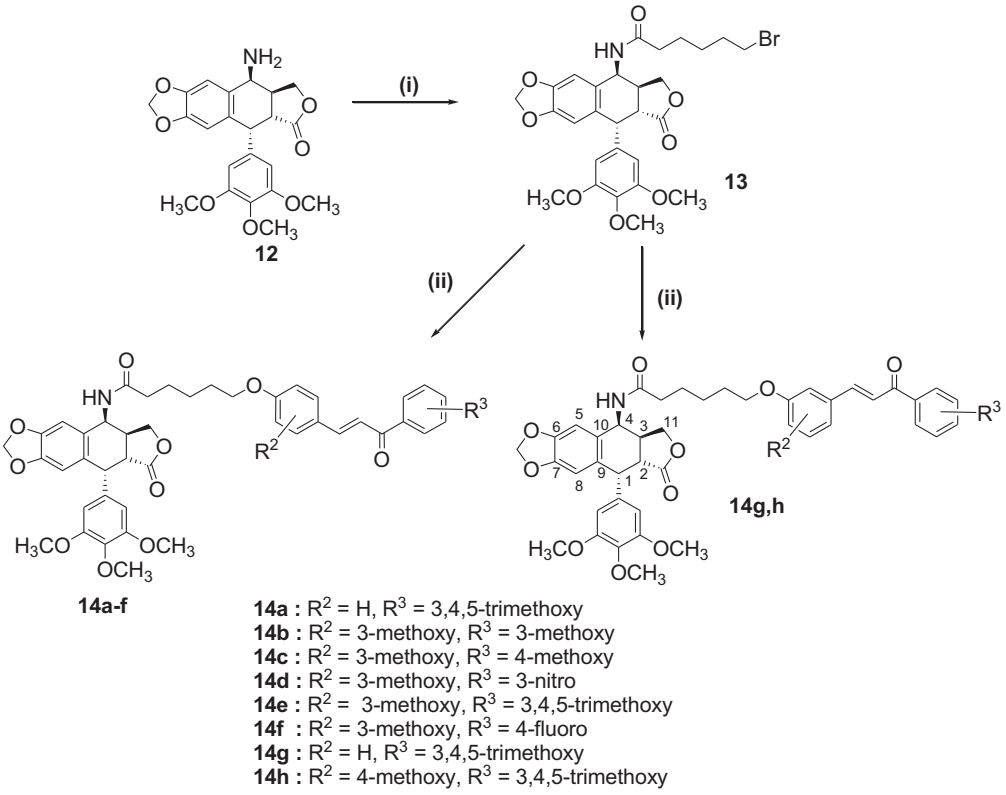
2.1. Chemistry

The synthesis of chalcone intermediates **9a**–**h** and **11a**–**h** has been carried out by synthetic sequence illustrated in Scheme 1. Claisen–Schmidt condensation of different acetophenones with benzaldehydes using ethanol in the presence of aqueous KOH provide chalcones **9a**–**h** predominantly with *E*-configuration. These chalcones undergo etherification of hydroxyl group with α-bromoethyl acetate by using K_2CO_3 as a base in dry DMF to afford the intermediates **10a**–**h**, which upon hydrolysis with $LiOH \cdot H_2O$ provide the chalcone acids **11a**–**h**. The synthesis of podophyllotoxin analogues **14a**–**h** and **15a**–**h** is described in Schemes 2 and 3. 4β-Aminopodophyllotoxin (**12**) has been synthesized as described in our previously reported procedure [32a,33a]. This upon treatment with 6-bromohexanoylchloride gives **13**, then followed by ether bond formation with **9a**–**h** provide the desired conjugates **14a**–**h** as depicted in Scheme 2. Chalcone acids **11a**–**h** on amide

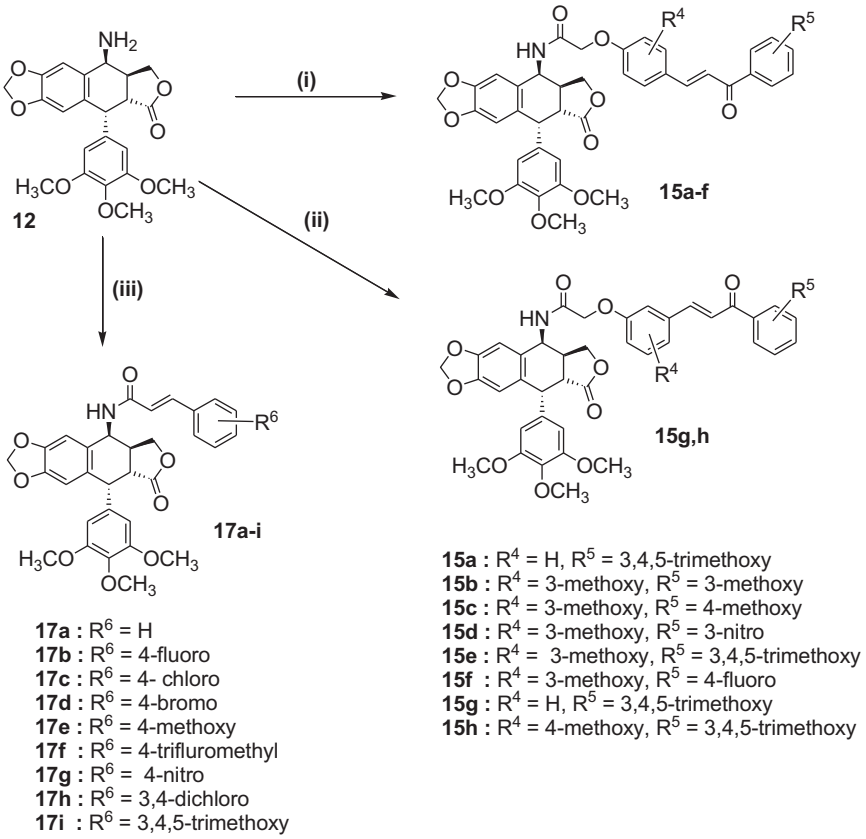


11a : R = H, R^1 = 3,4,5-trimethoxy
11b : R = 3-methoxy, R^1 = 3-methoxy
11c : R = 3-methoxy, R^1 = 4-methoxy
11d : R = 3-methoxy, R^1 = 3-nitro
11e : R = 3-methoxy, R^1 = 3,4,5-trimethoxy
11f : R = 3-methoxy, R^1 = 4-fluoro
11g : R = H, R^1 = 3,4,5-trimethoxy
11h : R = 4-methoxy, R^1 = 3,4,5-trimethoxy

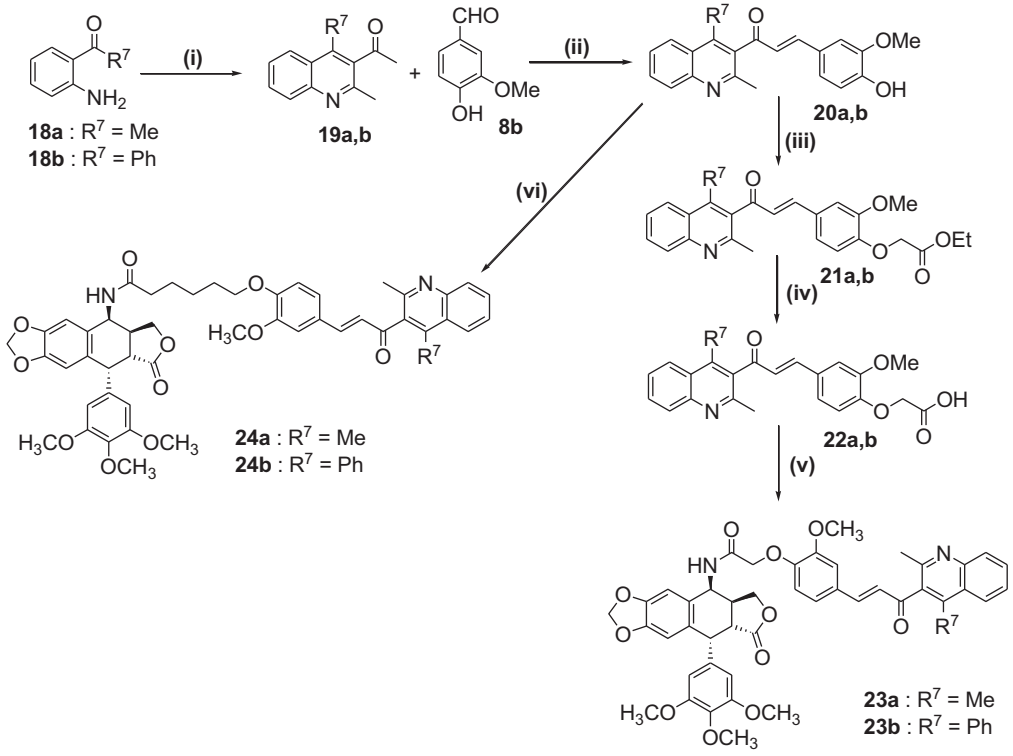
Scheme 1. Synthesis of **11a**–**h**. Reagents and conditions: (i) KOH, Ethanol, rt, 12 h; (ii) α-Bromoethyl acetate, K_2CO_3, DMF, rt, 12 h; (iii) $LiOH.H_2O$, THF, Water, rt, 12 h.



Scheme 2. Synthesis of **14a**–**h**. Reagents and conditions: (i) 6-Bromohexanoylchloride, TEA, DCM, rt, 8 h; (ii) **9a**–**h**, K_2CO_3, Acetone, Reflux, 12 h.



Scheme 3. Synthesis of **15a**–**h** and **17a**–**i**. Reagents and conditions: (i) **11a**–**f**, EDCI, HOBT, Dry DCM, rt, 12 h; (ii) **11g**,**h**, EDCI, HOBT, Dry DCM, rt, 12 h; (iii) *trans* Cinnamic acids **16a**–**i**, EDCI, HOBT, Dry DCM, rt, 12 h.



Scheme 4. Synthesis of **23a**,**b** and **24a**,**b**. Reagents and conditions: (i) 2,4-Pentanedione, Acetonitrile, HCl, rt, 12 h; (ii) KOH, Ethanol, rt, 12 h; (iii) α-Bromoethyl acetate, K_2CO_3, DMF, rt, 12 h; (iv) LiOH.H_2O, THF, Water, rt, 12 h; (v) Compound **12**, EDCI, HOBT, Dry DCM, rt, 12 h; (vi) Compound **13**, K_2CO_3, Acetone, Reflux, 12 h.

bond formation with **12** using EDCI/HOBt afford the required analogues **15a**–**h** in good yields as shown in Scheme 3. Precursor **12** on amide bond formation with different *trans* cinnamic acids (**16a**–**i**) using EDCI/HOBt afford 4β-cinnamido podophyllotoxin derivatives (**17a**–**i**) in good yields as shown in Scheme 3.

The synthesis of conjugates **23** and **24** is described in Scheme 4. 2-Aminoacetophenone or 2-aminobenzophenone is reacted with 2,4-pentanedione in the presence of acidic medium to give 3-acetylquinolines (**19**) which upon Claisen–Schmidt condensation with vanillin provide the quinolinochalcones (**20**). These chalcones upon etherification with α-bromoethyl acetate followed by hydrolysis provide the intermediates (**22**) which upon amide bond formation with precursor **12** using EDCI/HOBt afford the desired conjugates (**23**), whereas the conjugates **24** are prepared by etherification of chalcone intermediates **20** with podophyllotoxin intermediate (**13**) as shown in Scheme 4.

2.2. Evaluation of biological activity

2.2.1. Anticancer activity

The newly synthesized compounds (**14a**–**h**, **15a**–**h**, **17a**–**i**, **23a**,**b** and **24a**,**b**) were evaluated for their *in vitro* anticancer activity against a panel of five human cancer cell lines, A-549 (lung), A375 (melanoma), MCF-7 (breast), HT-29 (colon) and ACHN (renal) by employing MTT assay. Etoposide, podophyllotoxin and doxorubicin were used as reference drugs. The results are summarized in Table 1 and expressed as IC_{50} values. The *in vitro* screening results revealed that some of the compounds possess considerable anticancer activity. Chalcone-podophyllotoxin conjugates (**14** and **15**) showed moderate activity against different cancer cell lines (IC_{50}, 5.3–26.7 μM). There is no change in activity with the difference in the length of alkane chain spacer between chalcone and podophyllotoxin moieties. The quinolino-chalcone linked podophyllotoxins (**23** and **24**) showed promising activity with IC_{50} values ranging from 2.2 to 15.4 μM compared to compounds **14** and **15**.

Table 1
Anticancer activity data of compounds **14a**–**h**, **15a**–**h**, **23a**,**b**, **24a**,**b** and **17a**–**h**.

Compound	IC_{50} values (μM)				
	A–549[a]	A375[b]	MCF-7[c]	HT-29[d]	ACHN[e]
14a	21.5	18.4	24.8	15.3	16.5
14b	14.4	20.1	17.5	11.9	13.7
14c	19	13	12	16	10
14d	10.7	10.8	18.1	8.75	11.9
14e	13.6	9.8	10.2	12.1	19.5
14f	5.9	11.4	15.8	11.7	9.3
14g	14.7	11.5	8.3	21.1	20.8
14h	16.7	10.3	12.6	6.47	13.4
15a	19.1	25.8	24.2	12.4	10.18
15b	9.1	13.8	21.8	8.1	13.8
15c	8.3	9.3	16.2	16.9	16.1
15d	9	5.3	6.7	8.41	13.2
15e	10.7	7.8	14.9	9.54	8.51
15f	26.4	12.2	19.1	21.6	26.7
15g	16.8	18.2	24.4	15.6	9.1
15h	11.7	11.5	15.4	5.98	11.1
23a	15.4	14.5	13.8	12.3	10.8
23b	13.4	7.7	11.2	7.75	15.7
24a	10.6	10.3	8.6	11.8	10.7
24b	7.7	6.8	2.2	8.9	9.46
17a	2.7	13.4	19.7	2.36	3.91
17b	6.8	9.5	14.6	7.1	18.6
17c	8.8	5.7	13.7	11.4	7.54
17d	9.5	17.8	11.2	19.2	14.3
17e	7.7	19.1	15.7	17.6	17.8
17f	2.1	18	19.2	0.37	2.18
17g	8.2	14.5	10.1	18.1	12.8
17h	8.4	13.2	20.1	21	17.7
17i	7.9	14	17.7	8.34	13.1
Doxorubicin	2.18	5.51	2.02	1.06	0.79
Etoposide	2.34	1.39	0.68	1.81	7.61
Podophyllotoxin	3.75	2.62	1.18	0.78	2.12
16a	87	64	108	114	91
16f	56	91	142	75	128

[a] Lung cancer.
[b] Melanoma cancer.
[c] Breast cancer.
[d] Colon cancer.
[e] Renal cancer

The cinnamido-podophyllotoxin conjugates (**17a**–**i**) showed good activity against A-549 cancer cell line with IC_{50} values ranging from 2.1 to 9.5 μM (Table 1), however showed good to moderate activity against other cell lines. Moreover **17a** and **17f** showed significant activity against A-549 (IC_{50} of **17a** is 2.7 μM and **17f** is 2.1 μM), HT-29 (IC_{50} of **17a** is 2.36 μM and **17f** is 0.37 μM) and ACHN (IC_{50} of **17a** is 3.91 μM and **17f** is 2.18 μM) cancer cell lines whereas etoposide showed IC_{50} values 2.34 μM, 1.81 μM and 7.61 μM in respective cell lines. The IC_{50} values of these compounds revealed that the cinnamic acid moiety enhances the anticancer activity compared to the chalcone moiety upon linking through alkane spacer.

2.2.2. Hoechst staining

Apoptosis is one of the major pathways that lead to the process of cell death. Chromatin condensation and fragmented nuclei are known as the classic characteristics of apoptosis. It was considered of interest to investigate the apoptotic inducing effect of the two potent compounds (**17a** and **17f**) by Hoechst staining (H 33258) method in A-549 cancer cell line. Therefore cells were treated with **17a** and **17f** at 2 μM and 5 μM concentrations for 24 h wherein etoposide was used as the standard. Manual field quantification of apoptotic cells based on cytoplasmic condensation, presence of apoptotic bodies, nuclear fragmentation and relative fluorescence of the test compounds (**17a**, **17f** and etoposide) revealed that there was significant increase in the percentage of apoptotic cells (Fig. 2).

2.2.3. DNA fragmentation assay

DNA fragmentation is well known and a typical biochemical hallmark of apoptotic cell death. From the *in vitro* anticancer

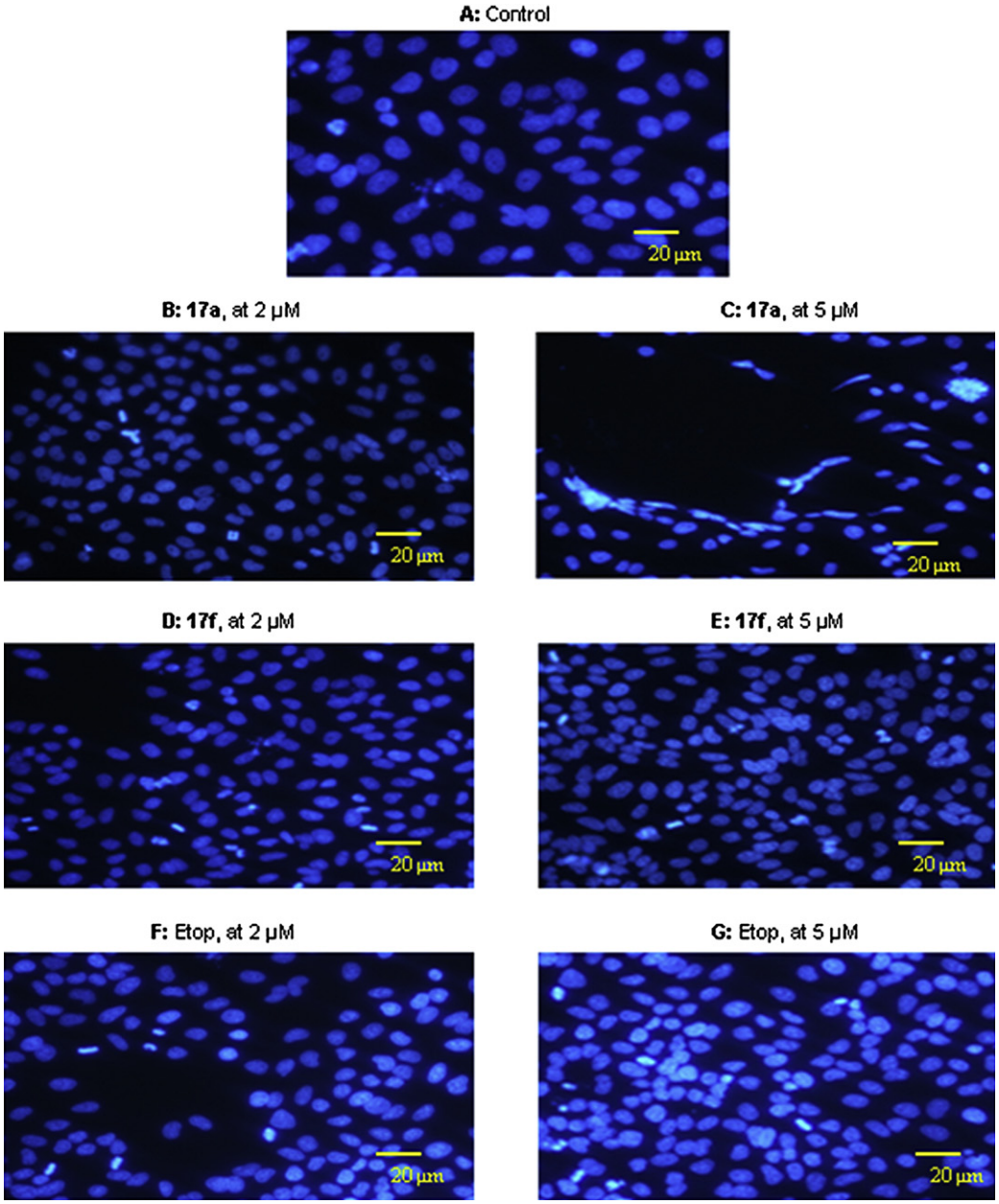


Fig. 2. Hoechst staining in A-549 lung cancer cell line, A: A-549 control cells, B: **17a** at 2 μM, C: **17a** at 5 μM, D: **17f** at 2 μM, E: **17f** at 5 μM and **F**: Etop (etoposide) at 2 μM, **G**: Etop (etoposide) at 5 μM. The scale bar is 20 μm.

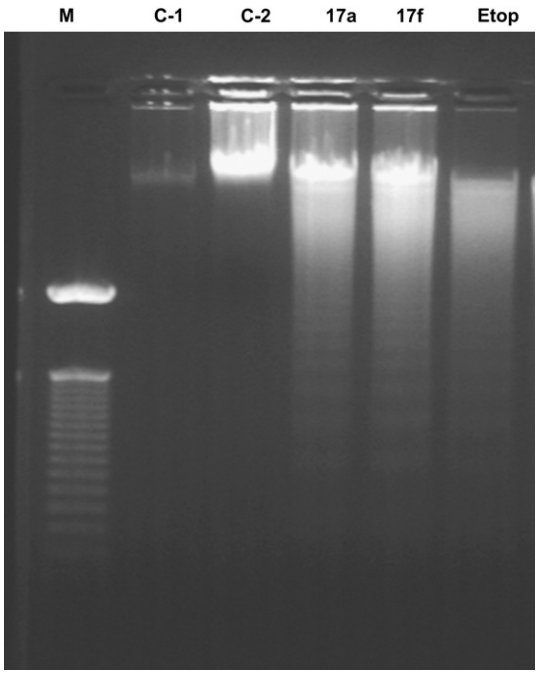
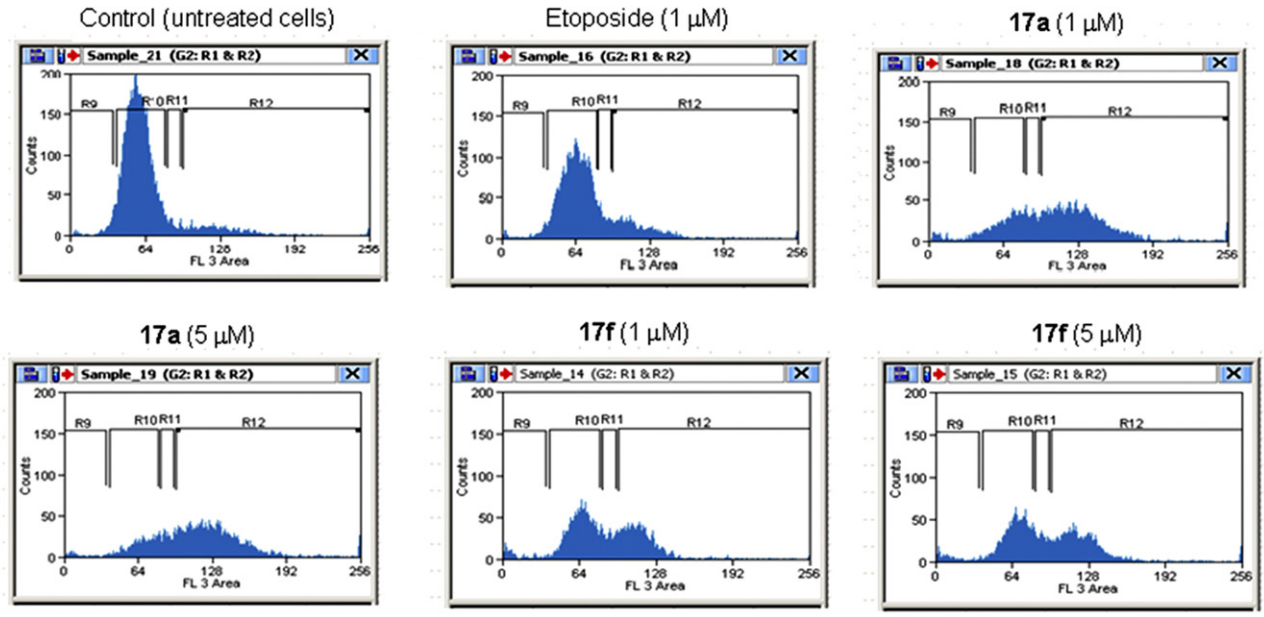


Fig. 3. DNA fragmentation of compounds **17a** and **17f** in A-549 lung cancer cells. Lane-1: Marker (50bp), Lane-2: C-1, untreated control DNA (1 μl), Lane-3: C-2, untreated control DNA (5 μl), Lane-4: **17a** at 5 μM, Lane-5: **17f** at 5 μM and Lane-6: Etop (etoposide) at 5 μM. Loaded DNA for **17a**, **17f** and etoposide is 5 μl.

studies it was observed that compounds **17a** and **17f** significantly inhibits the growth of human lung cancer cell line A-549. Therefore it was of interest to determine the mechanism of cell death in the same cell line. The DNA fragmentation analysis revealed that compounds **17a** and **17f** induced a discrete ladder pattern in A-549 cell line at 5 μM after 48 h of incubation thereby showing significant fragmentation. Etoposide also exhibits DNA fragmentation, however, no fragmentation was observed in untreated cells (Fig. 3).

2.2.4. Cell cycle analysis

On the basis of the results of anticancer data, detailed biological studies were focused on compounds **17a** and **17f**. With a view to further understand the mode of action of these compounds (**17a** and **17f**), we examined the effects on cell cycle by flow cytometry in A-549 cancer cells. In this study A-549 cells were treated with compounds **17a** and **17f** for 48 h at concentrations 1 μM and 5 μM. The data obtained clearly indicated that these compounds show G2/M cell cycle arrest as compared to the untreated control. These compounds (**17a** and **17f**) show 61% and 38% of cell accumulation in G2/M phase respectively at 1 μM concentration, whereas it exhibited 67%, 43% of cell accumulation in G2/M phase at 5 μM concentration (Fig. 4). However, etoposide showed 19% of cell accumulation in G2/M phase at 1 μM concentration and in control (untreated cells) 9% of G2/M phase was observed. Increase in cell cycle arrest at G2/M phase was observed upon treatment of A-549 cells by these compounds from 1 μM to 5 μM concentration.



Compound	Sub G1%	G0/G1%	S%	G2/M%
Control	2.74	83.43	2.74	9.27
17a (1 μM)	3.29	23.39	9.5	61.89
17a (5 μM)	2.62	18.65	8.64	67.78
17f (1 μM)	4.51	45.23	9.54	38.11
17f (5 μM)	4.43	39.84	10.16	43.39
Etoposide (1 μM)	2.89	69.82	7.23	19.21

Fig. 4. Flow cytometric analysis of compounds **17a**, **17f** and etoposide in A-549 lung cancer cell line.

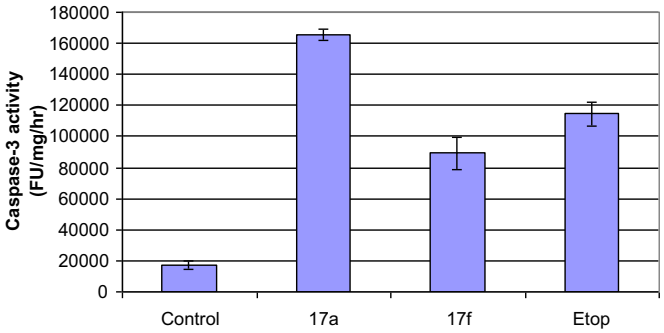


Fig. 5. Effect of compounds **17a** and **17f** on caspase-3 activity: A-549 cells were treated for 48 h with 2 μM concentration of compounds **17a** and **17f**. Etoposide (Etop) is used as a positive control. Values indicated are the mean ± SD of two different experiments performed in triplicates.

2.2.5. Caspase-3 activation assay

There are some reports [35–37] that the cell cycle arrest at G2/M phase takes place by the induction of cellular apoptosis. Hence, it was considered of interest to understand the correlation of cytotoxicity with that to apoptosis by **17a** and **17f**. Cysteine aspartase group, namely, caspases play a crucial role in the induction of apoptosis and amongst them caspase-3 happens to be one of the effecter caspase. Hence, we treated A-549 cells with **17a** and **17f** along with the positive control etoposide and examined the activation of caspase-3. The results indicate that there is nearly 4–8 fold induction in caspase-3 activity in cells treated with 2 μM concentration by these compounds. Interestingly under similar conditions, etoposide (2 μM) also induced the caspase activity by nearly 6-fold as compared to control as shown in Fig. 5. Therefore activation of caspase-3 by **17a** and **17f** indicate that they have the capacity to induce apoptosis in A-549 cells.

3. Conclusion

In conclusion, twenty nine congeners of 4β-alkylamidochalcone as well as 4β-cinnamido linked podophyllotoxins have been synthesized and evaluated for their anticancer potential against five human cancer cell lines (A-549, A375, MCF-7, HT-29 and ACHN). Some of these compounds exhibit significant *in vitro* anticancer activity at micro molar (μM) concentration. Two most potent compounds (**17a** and **17f**) exhibited promising anticancer activity (IC_{50}, 2.7 and 2.1 μM respectively) against A-549 cancer cell line. Flow cytometric analysis of these compounds arrested the cell cycle in the G2/M phase. Hoechst 33258 staining and DNA fragmentation assay revealed that these compounds induce cell death by apoptosis. Further, activation of caspase-3 also suggested that these compounds produce apoptotic cell death. Hence from this data it can be concluded that linking ofchalcone and cinnamic acid moieties with podophyllotoxin scaffold through amide bond and with alkane spacers has not only shown significant anticancer activity but has provided an insight for future direction in the development of such molecules.

4. Experimental

4.1. General methods

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) or Spectrochem Pvt. Ltd (Mumbai, India) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 GF-254, and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. 1H and C-13 NMR spectra were recorded on Gemini Varian-VXR-unity (200 MHz) or Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI + software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. High-resolution mass spectra (HRMS) were recorded on QSTAR XL Hybrid MS/MS mass spectrometer. Melting points were determined with an Electro thermal melting point apparatus, and are uncorrected.

*4.1.1. General procedure for the synthesis of compounds **9a–h***

Chalcones (**9a**, **9e**, **9g** and **9h**) were synthesized by means of a Claisen–Schmidt condensation reaction, as previously reported [20b,38]. To a stirred mixture of substituted acetophenone (1 mmol) and corresponding benzaldehyde (1.1 mmol) in ethanol (10 ml) was added 50% aqueous solution of potassium hydroxide (1 ml) and stirred for 6 h at room temperature. After completion of the reaction checked by TLC, the solvent was evaporated, neutralized with 1N HCl solution and extracted with ethyl acetate (2 × 50 ml). The combined organic fractions were washed with water followed by brine, dried over Na_2SO_4 and purified by column chromatography on silica gel using ethyl acetate and hexane to afford yellow solid.

*4.1.1.1. (E)-3-(4-Hydroxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**9a**).* Yellow solid; yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 15.1 Hz, 1H, db**H**), 7.57 (d, J = 9.0 Hz, 1H, Ar**H**), 7.36 (d, J = 15.1 Hz, 1H, db**H**), 7.27 (s, 2H, Ar**H**), 6.91 (d, J = 8.3 Hz, 1H, Ar**H**), 6.05 (br s, 1H, ArO**H**), 3.95 (s, 6H, −OC**H**$_3$), 3.93 (s, 3H, −OC**H**$_3$); ESI-MS: 315 $(M + H)^+$.

*4.1.1.2. (E)-3-(4-hydroxy-3-methoxyphenyl)-1-(3-methoxyphenyl) prop-2-en-1-one (**9b**).* Yellow solid; yield 71%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.7 (d, J = 15.67 Hz, 1H, db**H**), 7.52–7.58 (dd, J = 7.55, 1.51 Hz, 1H, Ar**H**), 7.49 (d, J = 2.64 Hz, 1H, Ar**H**), 7.3–7.42 (m, 2H, Ar**H**, db**H**), 7.11–7.21 (m, 2H, Ar**H**), 7.03–7.1 (dd, J = 8.1, 2 Hz, 1H, Ar**H**), 6.78 (d, J = 7.93 Hz, 1H, Ar**H**), 6.01 (br s, 1H, ArO**H**), 3.94 (s, 3H, −OC**H**$_3$), 3.87 (s, 3H, −OC**H**$_3$); ESI-MS: 285 $(M + H)^+$.

*4.1.1.3. (E)-3-(4-hydroxy-3-methoxyphenyl)-1-(4-methoxyphenyl) prop-2-en-1-one (**9c**).* Yellow solid; yield 70%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.04 (d, J = 8.87 Hz, 2H, Ar**H**), 7.75 (d, J = 15.48 Hz, 1H, db**H**), 7.4 (d, J = 15.48 Hz, 1H, db**H**), 7.19–7.25 (dd, J = 8.3, 1.71 Hz, 1H, Ar**H**), 7.13 (d, J = 1.51 Hz, 1H, Ar**H**), 6.92–7.03 (m, 3H, Ar**H**), 5.96 (br s, 1H, ArO**H**), 3.96 (s, 3H, −OC**H**$_3$), 3.89 (s, 3H, −OC**H**$_3$); ESI-MS: 285 $(M + H)^+$.

*4.1.1.4. (E)-3-(4-hydroxy-3-methoxyphenyl)-1-(3-nitrophenyl)prop-2-en-1-one (**9d**).* Yellow solid; yield 75%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.8 (s, 1H, Ar**H**), 8.4–8.44 (dd, J = 7.91, 2.96 Hz, 1H, Ar**H**), 8.32 (d, J = 6.92 Hz, 1H, Ar**H**), 7.8 (d, J = 15.83 Hz, 1H, db**H**), 7.69 (t, J = 7.91 Hz, 1H, Ar**H**), 7.33 (d, J = 15.83 Hz, 1H, db**H**), 7.23–7.27 (m, 1H, Ar**H**), 7.12 (d, J = 1.98 Hz, 1H, Ar**H**), 6.95 (d, J = 7.91 Hz, 1H, Ar**H**), 5.83 (br s, 1H, ArO**H**), 4.0 (s, 3H, −OC**H**$_3$); ESI-MS: 300 $(M + H)^+$.

*4.1.1.5. (E)-3-(4-hydroxy-3-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**9e**).* Yellow solid; yield 82%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68 (d, J = 15.86 Hz, 1H, db**H**), 7.27 (d, J = 15.86 Hz, 1H, db**H**), 7.16–7.23 (m, 3H, Ar**H**), 7.05 (s, 1H, Ar**H**), 6.89 (d, J = 8.3 Hz, 1H, Ar**H**), 6.16 (br s, 1H, ArO**H**), 3.96 (s, 9H, −OC**H**$_3$), 3.89 (s, 3H, −OC**H**$_3$); ESI-MS: 345 $(M + H)^+$.

*4.1.1.6. (E)-1-(4-Fluorophenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (**9f**).* Yellow solid; yield 67%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98–8.07 (m, 2H, Ar**H**, db**H**), 7.66 (d, J = 15.86 Hz, 1H, Ar**H**), 7.34 (d, J = 15.86 Hz, 1H, db**H**), 7.21–7.29 (m, 1H, Ar**H**), 7.17 (d, J = 8.3 Hz, 2H, Ar**H**), 7.06 (d, J = 1.51 Hz, 1H, Ar**H**), 6.96 (d, J = 8.3 Hz, 1H, Ar**H**), 3.96 (s, 3H, −OC**H**$_3$); ESI-MS: 273 (M + H)$^+$.

*4.1.1.7. (E)-3-(3-Hydroxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**9g**).* Yellow solid; yield 79%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, J = 15.79 Hz, 1H, db**H**), 7.45 (d, J = 15.79 Hz, 1H, db**H**), 7.25–7.34 (m, 3H, Ar**H**), 7.21 (m, 2H, Ar**H**), 6.9–6.98 (m, 1H, Ar**H**), 6.56 (br s, 1H, ArO**H**), 3.95 (s, 3H, −OC**H**$_3$), 3.93 (s, 6H, −OC**H**$_3$); ESI-MS: 315 (M + H)$^+$.

*4.1.1.8. (E)-3-(3-hydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**9h**).* Yellow solid; yield 85%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, J = 16.02 Hz, 1H, db**H**), 7.36 (d, J = 16.02 Hz, 1H, db**H**), 7.25–7.32 (m, 3H, Ar**H**), 7.14 (dd, J = 8.73, 2.18 Hz, 1H, Ar**H**), 6.89 (d, J = 8.7 Hz, 1H, Ar**H**), 5.74 (br s, 1H, ArO**H**), 3.96 (s, 9H, −OC**H**$_3$), 3.94 (s, 3H, −OC**H**$_3$); ESI-MS: 345 (M + H)$^+$.

*4.1.2. General procedure for the synthesis of compounds **10a–h***

To a solution of chalcone (**9a–h**) (1 mmol) in dry DMF (10 ml) was added, anhydrous K_2CO_3 (1 mmol), α-bromoethyl acetate (1.1 mmol) and the mixture was stirred at room temperature for 14 h. The reaction was monitored by TLC. After completion of the reaction K_2CO_3 was removed by filtration and diluted the filtrate with water and extracted with dichloromethane (2 × 20 ml). The organic phases were washed with water followed by brine solution, dried over Na_2SO_4 and evaporated under vacuum. The residue, thus obtained was purified by column chromatography using ethyl acetate and hexane to afford yellow solid.

*4.1.2.1. (E)-ethyl-2-(4-(3-oxo-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)phenoxy)acetate (**10a**).* Yellow solid; yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 15.86 Hz, 1H, db**H**), 7.59 (d, J = 9.06 Hz, 2H, Ar**H**), 7.32 (d, J = 15.86 Hz, 1H, db**H**), 7.22 (s, 2H, Ar**H**), 6.91 (d, J = 8.3 Hz, 2H, Ar**H**), 4.63 (s, 2H, -OC**H**$_2$CO-), 4.22–4.32 (q, 2H, −OC**H**$_2$−), 3.95 (s, 6H, −OC**H**$_3$), 3.9 (s, 3H, −OC**H**$_3$), 1.32 (t, J = 7.06 Hz, 3H, −C**H**$_3$); ESI-MS: 401 (M + H)$^+$.

*4.1.2.2. (E)-ethyl-2-(2-methoxy-4-(3-(3-methoxyphenyl)-3-oxoprop-1-en-1-yl)phenoxy)acetate (**10b**).* Yellow solid; yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.7 (d, J = 15.67 Hz, 1H, db**H**), 7.52–7.58 (dd, J = 7.55, 1.51 Hz, 1H, Ar**H**), 7.49 (d, J = 2.64 Hz, 1H, Ar**H**), 7.3–7.42 (m, 2H, Ar**H**, db**H**), 7.11–7.21 (m, 2H, Ar**H**), 7.03–7.1 (dd, J = 8.1, 2 Hz, 1H, Ar**H**), 6.78 (d, J = 7.93 Hz, 1H, Ar**H**), 4.68 (s, 2H, −OC**H**$_2$CO−), 4.22–4.31 (q, 2H, -OC**H**$_2$-), 3.94 (s, 3H, −OC**H**$_3$), 3.87 (s, 3H, −OC**H**$_3$), 1.3 (t, J = 7.17 Hz, 3H, -C**H**$_3$); ESI-MS: 371 (M + H)$^+$.

*4.1.2.3. (E)-ethyl-2-(2-methoxy-4-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)phenoxy)acetate (**10c**).* Yellow solid; yield 80%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.98 (d, J = 9.08 Hz, 2H, Ar**H**), 7.68 (d, J = 16.15 Hz, 1H, db**H**), 7.35 (d, J = 16.15 Hz, 1H, db**H**), 7.12–7.18 (m, 2H, Ar**H**), 6.93 (d, J = 9.08 Hz, 2H, Ar**H**), 6.8 (d, J = 8.07 Hz, 1H, Ar**H**), 4.67 (s, 2H, -OC**H**$_2$CO-), 4.21–4.29 (q, 2H, -OC**H**$_2$-), 3.94 (s, 3H, −OC**H**$_3$), 3.88 (s, 3H, −OC**H**$_3$), 1.3 (t, J = 7.06 Hz, 3H, -C**H**$_3$); ESI-MS: 371 (M + H)$^+$.

*4.1.2.4. (E)-ethyl-2-(2-methoxy-4-(3-(3-nitrophenyl)-3-oxoprop-1-en-1-yl)phenoxy)acetate (**10d**).* Yellow solid; yield 75%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.8 (s, 1H, Ar**H**), 8.4–8.46 (dd, J = 8.3, 2.26 Hz, 1H, Ar**H**), 8.3–8.35 (dd, J = 8.3, 1.51 Hz, 1H, Ar**H**), 7.8 (d, J = 15.86 Hz, 1H, db**H**), 7.7 (t, J = 8.3, 7.75 Hz, 1H, Ar**H**), 7.36 (d, J = 15.86 Hz, 1H, db**H**), 7.19–7.24 (dd, J = 8.3, 2.26 Hz, 1H, Ar**H**), 7.17 (d, J = 1.51 Hz, 1H, Ar**H**), 6.82 (d, J = 8.3 Hz, 1H, Ar**H**), 4.7 (s, 2H, −OC**H**$_2$CO−), 4.21–4.31 (q, 2H, −OC**H**$_2$−), 3.97 (s, 3H, −OC**H**$_3$), 1.31 (t, J = 7.55, 6.79 Hz, 3H, -C**H**$_3$); ESI-MS: 386 (M + H)$^+$.

*4.1.2.5. (E)-ethyl-2-(2-methoxy-4-(3-oxo-3-(3,4,5-trimethoxyphenyl) prop-1-en-1-yl)phenoxy)acetate (**10e**).* Yellow solid; yield 76%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J = 15.83 Hz, 1H, db**H**), 7.28 (d, J = 15.83 Hz, 1H, db**H**), 7.21 (s, 2H, Ar**H**), 7.17–7.2 (dd, J = 7.9, 1.91 Hz, 1H, Ar**H**), 7.14 (d, J = 1.91 Hz, 1H, Ar**H**), 6.82 (d, J = 8.9 Hz, 1H, Ar**H**), 4.68 (s, 2H, -OC**H**$_2$CO-), 4.22–4.29 (q, 2H, -OC**H**$_2$-), 3.94 (s, 6H, −OC**H**$_3$), 3.9 (s, 3H, −OC**H**$_3$), 1.3 (t, J = 6.92 Hz, 3H, −C**H**$_3$); ESI-MS: 431 (M + H)$^+$.

*4.1.2.6. (E)-ethyl-2-(4-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)acetate (**10f**).* Yellow solid; yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98–8.07 (m, 2H, Ar**H**), 7.66 (d, J = 15.86 Hz, 1H, db**H**), 7.34 (d, J = 15.86 Hz, 1H, db**H**), 7.21–7.29 (m, 1H, Ar**H**), 7.17 (d, J = 8.3 Hz, 2H, Ar**H**), 7.06 (d, J = 1.51 Hz, 1H, Ar**H**), 6.96 (d, J = 8.3 Hz, 1H, Ar**H**), 4.64 (s, 2H, -OC**H**$_2$CO-), 4.22–4.32 (q, 2H, -OC**H**$_2$-), 3.96 (s, 3H, −OC**H**$_3$), 1.31 (t, J = 7.06 Hz, 3H, −C**H**$_3$); ESI-MS: 359 (M + H)$^+$.

*4.1.2.7. (E)-ethyl-2-(3-(3-oxo-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)phenoxy)acetate (**10g**).* Yellow solid; yield 82%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.71 (d, J = 15.83 Hz, 1H, db**H**), 7.41 (d, J = 15.83 Hz, 1H, db**H**), 7.28–7.34 (m, 1H, Ar**H**), 7.23 (s, 2H, Ar**H**), 7.21–7.26 (m, 2H, Ar**H**), 7.16 (d, J = 2.26 Hz, 1H, Ar**H**), 6.88–6.93 (dd, J = 8.3, 2.26 Hz, 1H, Ar**H**), 4.63 (s, 2H, −OC**H**$_2$CO−), 4.23–4.3 (q, 2H, −OC**H**$_2$−), 3.94 (s, 6H, −OC**H**$_3$), 3.9 (s, 3H, −OC**H**$_3$), 1.31 (t, J = 6.92 Hz, 3H, −C**H**$_3$); ESI-MS: 401 (M + H)$^+$.

*4.1.2.8. (E)-ethyl-2-(2-methoxy-5-(3-oxo-3-(3,4,5-trimethoxyphenyl) prop-1-en-1-yl)phenoxy)acetate (**10h**).* Yellow solid; yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 15.67 Hz, 1H, db**H**), 7.36 (d, J = 15.67 Hz, 1H, db**H**), 7.27–7.33 (m, 3H, Ar**H**), 7.14–7.18 (dd, J = 7.83, 1.56 Hz, 1H, Ar**H**), 6.94 (d, J = 7.83 Hz, 1H, Ar**H**), 4.74 (s, 2H, −OC**H**$_2$CO−), 4.24–4.32 (q, 2H, −OC**H**$_2$−), 3.96 (s, 9H, −OC**H**$_3$), 3.94 (s, 3H, −OC**H**$_3$), 1.31 (t, J = 7.05 Hz, 3H, -C**H**$_3$); ESI-MS: 431 (M + H)$^+$.

*4.1.3. General procedure for the synthesis of compounds **11a–h***

To a solution of compound (**10a–h**) (1 mmol) in THF (15 ml) and water (2 ml), LiOH.H_2O (3 mmol) was added, and the mixture was stirred at room temperature for 12 h. The reaction was monitored by TLC using ethyl acetate. After completion of the reaction the solvent was removed under vacuum, neutralized with 1N HCl solution and extracted with dichloromethane (2 × 20 ml). The organic phases were washed with water followed by brine solution, dried over Na_2SO_4 and evaporated under vacuum to obtain crude compound which was purified by recrystalization by using ethyl acetate as solvent to obtain the pure product **11a–h** as yellow solid.

*4.1.3.1. (E)-2-(4-(3-oxo-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl) phenoxy)acetic acid (**11a**).* Yellow solid; yield 72%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.97 (br s, 1H, -COO**H**), 7.74 (d, J = 15.86 Hz, 1H, db**H**), 7.61 (d, J = 9.06 Hz, 2H, Ar**H**), 7.33 (d, J = 15.86 Hz, 1H, db**H**), 7.22 (s, 2H, Ar**H**), 6.92 (d, J = 8.3 Hz, 2H, Ar**H**), 4.65 (s, 2H, −OC**H**$_2$CO-), 3.95 (s, 6H, −OC**H**$_3$), 3.9 (s, 3H, −OC**H**$_3$); ESI-MS: 373 (M + H)$^+$.

*4.1.3.2. (E)-2-(2-methoxy-4-(3-(3-methoxyphenyl)-3-oxoprop-1-en-1-yl)phenoxy)acetic acid (**11b**).* Yellow solid; yield 70%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.94 (br s, 1H, -COO**H**), 7.7 (d, J = 15.67 Hz, 1H, db**H**), 7.51–7.58 (dd, J = 7.55, 1.51 Hz, 1H, Ar**H**), 7.5 (d, J = 2.64 Hz, 1H, Ar**H**), 7.31–7.42 (m, 2H, db**H**, Ar**H**), 7.13–7.22 (m, 2H, Ar**H**), 7.05–7.11 (dd, J = 8.1, 2 Hz, 1H, Ar**H**), 6.79 (d, J = 7.93 Hz, 1H, Ar**H**), 4.7 (s, 2H, -OC**H**$_2$CO-), 3.95 (s, 3H, −OC**H**$_3$), 3.87 (s, 3H, −OC**H**$_3$); ESI-MS: 343 (M + H)$^+$.

*4.1.3.3. (E)-2-(2-methoxy-4-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)phenoxy)acetic acid (**11c**).* Yellow solid; yield 69%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99 (d, *J* = 9.08 Hz, 2H, Ar**H**), 7.95 (br s, 1H, -COO**H**), 7.68 (d, *J* = 16.15 Hz, 1H, db**H**), 7.36 (d, *J* = 16.15 Hz, 1H, db**H**), 7.12–7.2 (m, 2H, Ar**H**), 6.95 (d, *J* = 9.08 Hz, 2H, Ar**H**), 6.81 (d, *J* = 8.07 Hz, 1H, Ar**H**), 4.68 (s, 2H, −OC**H**$_2$CO−), 3.95 (s, 3H, −OC**H**$_3$), 3.88 (s, 3H, −OC**H**$_3$); ESI-MS: 343 (M + H)$^+$.

*4.1.3.4. (E)-2-(2-methoxy-4-(3-(3-nitrophenyl)-3-oxoprop-1-en-1-yl)phenoxy)acetic acid (**11d**).* Yellow solid; yield 61%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.83 (s, 1H, Ar**H**), 8.42–8.47 (dd, *J* = 8.3, 2.26 Hz, 1H, Ar**H**), 8.31–8.35 (dd, *J* = 8.3, 1.51 Hz, 1H, Ar**H**), 8.12 (br s, 1H, −COO**H**), 7.82 (d, *J* = 15.86 Hz, 1H, db**H**), 7.7 (t, *J* = 8.3, 7.75 Hz, 1H, Ar**H**), 7.37 (d, *J* = 15.86 Hz, 1H, db**H**), 7.2–7.25 (dd, *J* = 8.3, 2.26 Hz, 1H, Ar**H**), 7.17 (d, *J* = 1.51 Hz, 1H, Ar**H**), 6.83 (d, *J* = 8.3 Hz, 1H, Ar**H**), 4.71 (s, 2H, −OC**H**$_2$CO−), 3.95 (s, 3H, −OC**H**$_3$); ESI-MS: 358 (M + H)$^+$.

*4.1.3.5. (E)-2-(2-methoxy-4-(3-oxo-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)phenoxy)acetic acid (**11e**).* Yellow solid; yield 76%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.97 (br s, 1H, -COO**H**), 7.68 (d, *J* = 15.83 Hz, 1H, db**H**), 7.3 (d, *J* = 15.83 Hz, 1H, db**H**), 7.22 (s, 2H, Ar**H**), 7.19–7.21 (dd, *J* = 7.9, 1.91 Hz, 1H, Ar**H**), 7.14 (d, *J* = 1.91 Hz, 1H, Ar**H**), 6.84 (d, *J* = 8.9 Hz, 1H, Ar**H**), 4.7 (s, 2H, -OC**H**$_2$CO-), 3.94 (s, 6H, −OC**H**$_3$), 3.9 (s, 3H, −OC**H**$_3$); ESI-MS: 403 (M + H)$^+$.

*4.1.3.6. (E)-2-(4-(3-(4-Fluorophenyl)-3-oxoprop-1-en-1-yl)-2-methoxyphenoxy)acetic acid (**11f**).* Yellow solid; yield 66%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8–8.07 (m, 2H, Ar**H**), 7.99 (br s, 1H, −COO**H**), 7.67 (d, *J* = 15.86 Hz, 1H, db**H**), 7.36 (d, *J* = 15.86 Hz, 1H, db**H**), 7.22–7.29 (m, 1H, Ar**H**), 7.17 (d, *J* = 8.3 Hz, 2H, Ar**H**), 7.08 (d, *J* = 1.51 Hz, 1H, Ar**H**), 6.98 (d, *J* = 8.3 Hz, 1H, Ar**H**), 4.67 (s, 2H, −OC**H**$_2$CO−), 3.95 (s, 3H, −OC**H**$_3$); ESI-MS: 331 (M + H)$^+$.

*4.1.3.7. (E)-2-(3-(3-oxo-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl) phenoxy)acetic acid (**11g**).* Yellow solid; yield 72%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96 (br s, 1H, -COO**H**), 7.72 (d, *J* = 15.83 Hz, 1H, db**H**), 7.41 (d, *J* = 15.83 Hz, 1H, db**H**), 7.29–7.36 (m, 1H, Ar**H**), 7.24 (s, 2H, Ar**H**), 7.22–7.28 (m, 2H, Ar**H**), 7.17 (d, *J* = 2.26 Hz, 1H, Ar**H**), 6.9–6.95 (dd, *J* = 8.3, 2.26 Hz, 1H, Ar**H**), 4.65 (s, 2H, −OC**H**$_2$CO−), 3.95 (s, 6H, −OC**H**$_3$), 3.91 (s, 3H, −OC**H**$_3$); ESI-MS: 373 (M + H)$^+$.

*4.1.3.8. (E)-2-(2-methoxy-5-(3-oxo-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)phenoxy)acetic acid (**11h**).* Yellow solid; yield 69%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (br s, 1H, -COO**H**), 7.75 (d, *J* = 15.67 Hz, 1H, db**H**), 7.37 (d, *J* = 15.67 Hz, 1H, db**H**), 7.28–7.33 (m, 3H, Ar**H**), 7.14–7.19 (dd, *J* = 7.83, 1.56 Hz, 1H, Ar**H**), 6.96 (d, *J* = 7.83 Hz, 1H, Ar**H**), 4.75 (s, 2H, −OC**H**$_2$CO−), 3.97 (s, 9H, −OC**H**$_3$), 3.95 (s, 3H, −OC**H**$_3$); ESI-MS: 403 (M + H)$^+$.

*4.1.4. 4β-[6-Bromohexamido]-4-desoxy-podophyllotoxin (**13**)*

To a solution of 6-bromohaxanoic acid (1 mmol) in dry dichloromethane (20 ml) was added oxalyl chloride (1.5 mmol), and 2-3 drops of DMF at 0 °C. Reaction mixture was stirred for 6–8 h at room temperature. After completion of the reaction checked by TLC, the solvent was evaporated under vacuum to get 6-bromohexanoyl chloride as yellow solid. Dissolved the acid chloride in dry dichloromethane (20 ml) and was added compound **12** (1 mmol) and triethylamine (2 mmol) at 0 °C. Reaction mixture was stirred for 8–9 h at room temperature. After completion of reaction, water (20 ml) was added and compound was extracted with dichloromethane (2 × 20 ml). The organic phases were washed with water followed by brine solution, dried over Na_2SO_4 and evaporated under vacuum to obtain crude compound which was purified by column chromatography by using ethyl acetate and hexane as mobile phase to obtain the pure product **13** as solid.

White solid; yield 71%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.74 (s, 1H, Ar**H**), 6.47 (s, 1H, Ar**H**), 6.2 (s, 2H, Ar**H**), 5.96–6.01 (m, 3H, −OC**H**$_2$O−, −N**H**), 4.53 (d, *J* = 4.7 Hz, 1H, 1-**H**), 4.31–4.48 (m, 2H, 11-**H**), 3.94 (d, *J* = 6.04 Hz, 1H, 4-**H**), 3.74 (s, 3H, −OC**H**$_3$), 3.71 (s, 6H, −OC**H**$_3$), 3.51 (t, *J* = 6.6 Hz, 1H, −C**H**$_2$Br), 2.82–2.94 (m, 1H, 3-**H**), 2.72–2.83 (dd, *J* = 14.3, 4.7 Hz, 1H, 2-**H**), 2.2 (t, *J* = 7.3, 7.1 Hz, 1H, −C**H**$_2$CO−), 1.79–1.93 (m, 2H, −C**H**$_2$−), 1.59–1.74 (m, 2H, −C**H**$_2$−), 1.4–1.54 (m, 2H, −C**H**$_2$−); ESI-MS: 591 (M + H)$^+$.

*4.1.5. General procedure for the synthesis of compounds **14a**–**h***

To a solution of the compound **13** (1 mmol) and corresponding chalcone **9a**–**h** (1 mmol) in acetone (15 ml), K_2CO_3 (1 mmol) was added and the mixture stirred at reflux for 18 h. The reaction was monitored by TLC. After completion of the reaction K_2CO_3 was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate and hexane to afford solid.

*4.1.5.1. 4β-[6-{4-[(E)-3-Oxo-3-(3,4,5-trimethoxyphenyl)-1-propenyl] phenoxy}hexanamide]-4-desoxy-podophyllotoxin (**14a**).* Yellow solid, yield 75%; mp: 242–245 °C; $[\alpha]_D^{25}$ = −128.1 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, *J* = 15.1 Hz, 1H, db**H**), 7.59 (d, *J* = 9.06 Hz, 2H, Ar**H**), 7.35 (d, *J* = 15.1 Hz, 1H, db**H**), 7.27 (s, 2H, Ar**H**), 6.92 (d, *J* = 9.06 Hz, 2H, Ar**H**), 6.74 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.37 (s, 2H, Ar**H**), 5.91–5.97 (m, 3H, -OC**H**$_2$O-, -N**H**), 4.59 (d, *J* = 3.02 Hz, 1H, 1-**H**), 4.29–4.42 (m, 2H, 11-**H**), 4.02 (t, *J* = 6.04 Hz, 2H, -C**H**$_2$O-), 3.95 (s, 6H, −OC**H**$_3$), 3.94 (s, 3H, −OC**H**$_3$), 3.9 (d, *J* = 6.04 Hz, 1H, 4-**H**), 3.84 (s, 3H, −OC**H**$_3$), 3.81 (s, 6H, −OC**H**$_3$), 3.27–3.33 (dd, *J* = 9.82, 3.02 Hz, 1H, 2-**H**), 3.15–3.25 (m, 1H, 3-**H**), 2.28 (t, *J* = 7.55, 6.79 Hz, 2H, −C**H**$_2$CO−), 1.66–1.91 (m, 4H, −C**H**$_2$−), 1.46–1.51 (m, 2H, −C**H**$_2$−); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.41, 174.34, 167.95, 158.86, 153.25, 152.32, 148.63, 147.45, 143.15, 142.84, 137.64, 134.56, 133.78, 132.45, 130.43, 129.73, 128.24, 120.71, 115.32, 110.24, 108.97, 108.17, 106.42, 101.47, 68.86, 66.28, 60.94, 60.23, 56.37, 56.02, 47.58, 43.37, 41.13, 37.87, 28.04, 26.74, 25.19, 25.48; ESI-MS: 824 (M + H)$^+$; HRMS calcd for $C_{46}H_{50}NO_{13}$, 824.2642, found 824.2645.

*4.1.5.2. 4β-[6-{2-Methoxy-4-[(E)-3-(3-methoxyphenyl)-3-oxo-1-propenyl]phenoxy} hexanamide]-4-desoxy-podophyllotoxin (**14b**).* Yellow solid, yield 78%; mp: 220–223 °C; $[\alpha]_D^{25}$ = −124.5 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75 (d, *J* = 16.11 Hz, 1H, db**H**), 7.6 (d, *J* = 8.05 Hz, 1H, Ar**H**), 7.54 (d, *J* = 2.19 Hz, 1H, Ar**H**), 7.31–7.46 (m, 2H, Ar**H**, db**H**), 7.1–7.24 (m, 2H, Ar**H**), 6.89 (d, *J* = 8.05 Hz, 1H, Ar**H**), 6.7–6.81 (m, 2H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.36 (s, 2H, Ar**H**), 5.88–6.03 (m, 3H, −OC**H**$_2$O−, −N**H**), 4.57 (d, *J* = 4.39 Hz, 1H, 1-**H**), 4.25–4.45 (m, 2H, 11-**H**), 4.08 (t, *J* = 7.32, 6.59 Hz, 2H, −C**H**$_2$O−), 3.91 (s, 6H, −OC**H**$_3$), 3.89 (d, *J* = 5.23 Hz, 1H, 4-**H**), 3.83 (s, 3H, −OC**H**$_3$), 3.81 (s, 6H, −OC**H**$_3$), 3.28–3.36 (dd, *J* = 9.52, 4.39 Hz, 1H, 2-**H**), 3.16–3.27 (m, 1H, 3-**H**), 2.27 (t, *J* = 6.59, 5.86 Hz, 2H, −C**H**$_2$CO−), 1.81–1.9 (m, 2H, −C**H**$_2$−), 1.66–1.77 (m, 2H, -C**H**$_2$-), 1.41–1.52 (m, 2H, −C**H**$_2$−); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.15, 174.18, 168.47, 159.93, 152.68, 149.85, 148.83, 148.24, 147.35, 143.69, 139.87, 137.46, 134.48, 132.2, 130.61, 129.47, 128.77, 122.38, 121.48, 120.88, 119.25, 116.8, 112.64, 111.46, 109.92, 109.05, 108.21, 101.43, 68.4, 67.79, 60.94, 56.35, 55.87, 55.25, 47.57, 43.42, 41.87, 37.28, 28.93, 26.34, 25.39, 25.62; ESI-MS: 794 (M + H)$^+$; HRMS calcd for $C_{45}H_{48}NO_{12}$, 794.1208, found 794.1199.

*4.1.5.3. 4β-[6-{2-Methoxy-4-[(E)-3-(4-methoxyphenyl)-3-oxo-1-propenyl]phenoxy} hexanamide]-4-desoxy-podophyllotoxin (**14c**).* Yellow solid, yield 72%; mp: 219–222 °C; $[\alpha]_D^{25}$ = −121.8 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.68 Hz, 2H, Ar**H**), 7.74 (d, *J* = 15.48 Hz, 1H, db**H**), 7.4 (d, *J* = 15.48 Hz, 1H, db**H**), 7.17–7.24 (dd, *J* = 8.12, 2.2 Hz, 1H, Ar**H**), 7.15 (d, *J* = 2.2 Hz, 1H, Ar**H**), 6.98 (d, *J* = 8.87 Hz, 2H, Ar**H**), 6.88 (d, *J* = 8.3 Hz, 1H, Ar**H**), 6.74 (s, 1H, Ar**H**),

6.54 (s, 1H, Ar**H**), 6.36 (s, 2H, Ar**H**), 5.83–5.98 (m, 3H, −OC**H**$_2$O−, −N**H**), 4.56 (d, J = 3.8 Hz, 1H, 1-**H**), 4.28–4.2 (m, 2H, 11-**H**), 4.06 (t, J = 6.61, 6.42 Hz, 2H, −C**H**$_2$O−), 3.9 (s, 3H, −OC**H**$_3$), 3.89 (s, 3H, −OC**H**$_3$), 3.87 (d, J = 5.24 Hz, 1H, 4-**H**), 3.83 (s, 3H, −OC**H**$_3$), 3.8 (s, 6H, −OC**H**$_3$), 3.29–3.37 (dd, J = 9.82, 3.8 Hz, 1H, 2-**H**), 3.14–3.28 (m, 1H, 3-**H**), 2.28 (t, J = 7.55 Hz, 2H, −C**H**$_2$CO−), 1.66–1.94 (m, 4H, −C**H**$_2$−), 1.45–1.59 (m, 2H, −C**H**$_2$−); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.02, 174.09, 168.43, 163.95, 152.23, 149.3, 148.65, 148.28, 147.67, 143.85, 137.54, 134.64, 132.56, 130.75, 130.36, 130.98, 128.44, 122.38, 121.3, 116.74, 113.39, 111.74, 109.94, 109.12, 108.25, 101.6, 70.64, 68.35, 60.57, 56.15, 55.67, 55.32, 47.57, 43.63, 41.08, 37.72, 28.21, 26.74, 25.6, 25.53; ESI-MS: 794 $(M + H)^+$; HRMS calcd for $C_{45}H_{48}NO_{12}$, 794.1215, found 794.1211.

*4.1.5.4. 4β-[6-{2-Methoxy-4-[(E)-3-(3-nitrophenyl)-3-oxo-1-propenyl]phenoxy} hexanamide]-4-desoxy-podophyllotoxin (**14d**).* Yellow solid, yield 65%; mp: 257–260 °C; $[\alpha]_D^{25} = -118.6$ (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.83 (s, 1H, Ar**H**), 8.41–8.47 (dd, J = 8.68, 2.26 Hz, 1H, Ar**H**), 8.32–8.38 (dd, J = 7.55, 1.51 Hz, 1H, Ar**H**), 7.84 (d, J = 15.48 Hz, 1H, db**H**), 7.71 (t, J = 7.93 Hz, 1H, Ar**H**), 7.37 (d, J = 15.48 Hz, 1H, db**H**), 7.23–7.26 (m, 1H, Ar**H**), 7.17 (d, J = 2.06 Hz, 1H, Ar**H**), 6.91 (d, J = 8.3 Hz, 1H, Ar**H**), 6.74 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.36 (s, 2H, Ar**H**), 5.91–5.99 (m, 3H, −OC**H**$_2$O−, −N**H**), 4.59 (d, J = 3.8 Hz, 1H, 1-**H**), 4.3–4.41 (m, 2H, 11-**H**), 4.09 (t, J = 6.61, 6.23 Hz, 2H, −C**H**$_2$O−), 3.93 (s, 3H, −OC**H**$_3$),3.88 (d, J = 5.54 Hz, 1H, 4-**H**), 3.83 (s, 3H, −OC**H**$_3$), 3.81 (s, 6H, −OC**H**$_3$), 3.27–3.34 (dd, J = 9.81, 3.8 Hz, 1H, 2-**H**), 3.15–3.26 (m, 1H, 3-**H**), 2.29 (t, J = 7.36 Hz, 2H, −C**H**$_2$CO−), 1.85–1.87 (m, 2H, −C**H**$_2$−), 1.69–1.82 (m, 2H, −C**H**$_2$−), 1.49–1.57 (m, 2H, −C**H**$_2$−); ESI-MS: 809 $(M + H)^+$; HRMS calcd for $C_{44}H_{45}N_2O_{13}$, 809.1258, found 809.1245.

*4.1.5.5. 4β-[6-{2-Methoxy-4-[(E)-3-(3,4,5-trimethoxyphenyl)-3-oxo-1-propenyl]phenoxy} hexanamide]-4-desoxy-podophyllotoxin (**14e**).* Yellow solid, yield 77%; mp: 245–248 °C; $[\alpha]_D^{25} = -127.1$ (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (d, J = 15.48 Hz, 1H, db**H**), 7.32 (d, J = 15.48 Hz, 1H, db**H**), 7.21–7.27 (m, 3H, Ar**H**), 7.14 (d, J = 1.88 Hz, 1H, Ar**H**), 6.9 (d, J = 8.3 Hz, 1H, Ar**H**), 6.74 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.36 (s, 2sH, Ar**H**), 5.91–5.97 (m, 3H, −OC**H**$_2$O−, −N**H**), 4.55 (d, J = 3.39 Hz, 1H, 1-**H**), 4.51–4.43 (m, 2H, 11-**H**), 4.08 (t, J = 6.42 Hz, 2H, −C**H**$_2$O−), 3.95 (s, 6H, −OC**H**$_3$), 3.94 (s, 3H, −OC**H**$_3$), 3.88 (s, 3H, −OC**H**$_3$), 3.86 (d, J = 5.1 Hz, 1H, 4-**H**), 3.83 (s, 3H, −OCH3), 3.81 (s, 6H, −OCH3), 3.27–3.35 (dd, J = 9.82, 3.39 Hz, 1H, 2-**H**), 3.14–3.27 (m, 1H, 3-**H**), 2.28 (t, J = 7.74, 7.16 Hz, 2H, −C**H**$_2$CO−), 1.83–1.96 (m, 2H, −C**H**$_2$−), 1.67–1.81 (m, 2H, −C**H**$_2$−), 1.46–1.58 (m, 2H, −C**H**$_2$−); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.41, 178.5, 173.38, 153.5, 153.07, 149.41, 147.71, 147.26, 145, 142.31, 138.36, 133.73, 130.85, 130.47, 128.36, 127.7, 122.94, 119.68, 112.46, 111.13, 109.86, 106.54, 106.09, 104.89, 101.29, 68.76, 68.64, 60.92, 60.78, 56.4, 56.16, 47.92, 45.26, 44.59, 38.08, 36.44, 28.65, 27.61, 25.62, 25.29; ESI-MS: 854 $(M + H)^+$; HRMS calcd for $C_{47}H_{52}NO_{14}$, 854.1095, found 854.1086.

*4.1.5.6. 4β-[6-{2-Methoxy-4-[(E)-3-(4-fluorophenyl)-3-oxo-1-propenyl]phenoxy} hexanamide]-4-desoxy-podophyllotoxin (**14f**).* Yellow solid, yield 73%; mp: 214–217 °C; $[\alpha]_D^{25} = -120.4$ (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96–8.09 (m, 2H, Ar**H**), 7.7 (d, J = 15.86 Hz, 1H, db**H**), 7.31 (d, J = 15.86 Hz, 1H, db**H**), 7.2–7.25 (m, 1H, Ar**H**), 7.09 (d, J = 2.26 Hz, 1H, Ar**H**), 7.17 (d, J = 9.06 Hz, 2H, Ar**H**), 6.97 (d, J = 8.3 Hz, 1H, Ar**H**), 6.7 (s, 1H, Ar**H**), 6.49 (s, 1H, Ar**H**), 6.31 (s, 2H, Ar**H**), 5.9–5.98 (m, 3H, −OC**H**$_2$O−, −N**H**), 4.57 (d, J = 3.12 Hz, 1H, 1-**H**), 4.22–4.42 (m, 2H, 11-**H**), 4.04 (t, J = 6.04 Hz, 2H, −C**H**$_2$O−), 3.88 (s, 3H, −OCH3), 3.85 (d, J = 5.4 Hz, 1H, 4-**H**), 3.81 (s, 3H, −OCH3), 3.8 (s, 6H, −OCH3), 3.16–3.23 (dd, J = 9.8, 3.12 Hz, 1H, 2-**H**), 3.07–3.15 (m, 1H, 3-**H**), 2.26 (t, J = 6.79, 5.28 Hz, 2H, −C**H**$_2$CO−), 1.81–1.93 (m, 2H, −C**H**$_2$−), 1.63–1.8 (m, 2H, −C**H**$_2$−), 1.51–1.6 (m, 2H, −C**H**$_2$−); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.94, 174.11, 168.27, 152.67, 149.79, 148.87, 148.23, 147.59, 144.12, 137.21, 134.67, 132.23, 131.24, 130.89, 130.35, 128.41, 122.37, 121.27, 116.37, 116.05, 115.76, 111.85, 109.91, 109.14, 108.08, 101.44, 68.87, 67.42, 60.23, 56.97, 55.73, 47.37, 43.79, 41.46, 37.23, 28.87, 26.54, 25.61, 25.38; ESI-MS: 782 $(M + H)^+$; HRMS calcd for $C_{44}H_{45}FNO_{11}$, 782.1185, found 782.1173.

*4.1.5.7. 4β-[6-{3-[(E)-3-Oxo-3-(3,4,5-trimethoxyphenyl)-1-propenyl] phenoxy} hexanamide]-4-desoxy-podophyllotoxin (**14g**).* Yellow solid, yield 70%; mp: 235–237 °C; $[\alpha]_D^{25} = -127.6$ (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (d, J = 15.67 Hz, 1H, db**H**), 7.45 (d, J = 15.67 Hz, 1H, db**H**), 7.33 (t, J = 7.93, 7.74 Hz, 1H, Ar**H**), 7.27 (s, 2H, Ar**H**), 7.21–7.26 (m, 1H, Ar**H**), 7.15 (d, J = 2.07 Hz, 1H, Ar**H**), 6.92–6.98 (dd, J = 7.93, 2.26 Hz, 1H, Ar**H**), 6.74 (s, 1H, Ar**H**), 6.53 (s, 1H, Ar**H**), 6.36 (s, 2H, Ar**H**), 5.9–6.01 (m, 3H, −OC**H**$_2$O−, −N**H**), 4.59 (d, J = 3.39 Hz, 1H, 1-**H**), 4.3–4.44 (m, 2H, 11-**H**), 4.02 (t, J = 6.42, 6.23 Hz, 2H, −C**H**$_2$O−), 3.95 (s, 6H, −OCH3), 3.94 (s, 3H, −OCH3), 3.85 (d, J = 6.04 Hz, 1H, 4-**H**), 3.83 (s, 3H, −OCH3), 3.81 (s, 6H, −OCH3), 3.27–3.33 (dd, J = 10.1, 3.39 Hz, 1H, 2-**H**), 3.15–3.25 (m, 1H, 3-**H**), 2.28 (t, J = 7.55 Hz, 2H, −C**H**$_2$CO−), 1.69–1.89 (m, 4H, −C**H**$_2$−), 1.49–1.58 (m, 2H, −C**H**$_2$−); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.14, 174.13, 168.23, 157.28, 153.45, 152.55, 148.64, 147.42, 143.18, 142.35, 137.24, 136.89, 134.57, 133.24, 132.35, 130.48, 128.69, 122.86, 122.23, 116.56, 114.82, 110.15, 108.58, 108.1, 106.08, 101.6, 68.48, 67.35, 60.85, 60.32, 56.74, 56.07, 47.21, 43.88, 41.45, 37.34, 28.64, 26.35, 25.78, 25.32; ESI-MS: 824 $(M + H)^+$; HRMS calcd for $C_{46}H_{50}NO_{13}$, 824.1908, found 824.1925.

*4.1.5.8. 4β-[6-{2-Methoxy-5-[(E)-3-oxo-3-(3,4,5-trimethoxyphenyl)-1-propenyl]phenoxy} hexanamide]-4-desoxy-podophyllotoxin (**14h**).* Yellow solid, yield 71%; mp: 241–243 °C; $[\alpha]_D^{25} = -119.5$ (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73 (d, J = 15.61 Hz, 1H, db**H**), 7.32 (d, J = 15.61 Hz, 1H, db**H**), 7.22–7.29 (m, 3H, Ar**H**), 7.16 (d, J = 2.08 Hz, 1H, Ar**H**), 6.9 (d, J = 8.32 Hz, 1H, Ar**H**), 6.74 (s, 1H, Ar**H**), 6.53 (s, 1H, Ar**H**), 6.35 (s, 2H, Ar**H**), 5.91–5.99 (m, 3H, −OC**H**$_2$O−, −N**H**), 4.59 (d, J = 3.12 Hz, 1H, 1-**H**), 4.29–4.41 (m, 2H, 11-**H**), 4.07 (t, J = 6.24 Hz, 2H, −C**H**$_2$O−), 3.94 (s, 6H, −OCH3), 3.93 (s, 3H, −OCH3), 3.91 (s, 3H, −OCH3), 3.88 (d, J = 5.2 Hz, 1H, 4-**H**), 3.83 (s, 3H, −OCH3), 3.8 (s, 6H, −OCH3), 3.29–3.34 (dd, J = 10.41, 3.12 Hz, 1H, 2-**H**), 3.17–3.26 (m, 1H, 3-**H**), 2.29 (t, J = 7.28 Hz, 2H, −C**H**$_2$CO−), 1.85–1.94 (m, 2H, −C**H**$_2$−), 1.66–1.81 (m, 2H, −C**H**$_2$−), 1.51–1.59 (m, 2H, −C**H**$_2$−); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.52, 173.63, 168.57, 153.83, 152.92, 151.37, 148.4, 147.63, 147.02, 143.18, 142.49, 137.1, 135.62, 133.3, 132.58, 128.41, 124.43, 120.12, 116.23, 112.4, 109.98, 109.07, 108.86, 108.03, 106.25, 101.3, 68.97, 68.32, 60.92, 60.76, 56.42, 56.15, 47.62, 45.64, 43.25, 39.07, 37.44, 28.12, 26.81, 25.6, 25.35; ESI-MS: 854 $(M + H)^+$; HRMS calcd for $C_{47}H_{52}NO_{14}$, 854.1091, found 854.1075.

*4.1.6. General procedure for the synthesis of compounds **15a**–**h***

To a solution of compound **12** (1.0 mmol) in dichloromethane (20 ml) was added EDCI.HCl (1.1 mmol) and HOBt (0.1 mmol). Then added corresponding chalcone acids (**11a**–**h**) (1.0 mmol) and the reaction mixture was stirred at room temperature for 24 h. The reaction was monitored by TLC. After completion of reaction, water was added to reaction mixture and extracted with dichloromethane (2 × 30 ml). The solvent was evaporated under reduced pressure to afford the crude product which was further purified by column chromatography on silica gel using ethyl acetate and hexane as solvent system to obtain the pure products as solids.

*4.1.6.1. 4β-[2-{4-[(E)-3-Oxo-3-(3,4,5-trimethoxyphenyl)-1-propenyl] phenoxy} acetamide]-4-desoxy-podophyllotoxin (**15a**).* Yellow solid, yield 61%; mp: 246–248 °C; $[\alpha]_D^{25} = -120.5$ (c = 0.5 in $CHCl_3$); ^{1}H

NMR (200 MHz, $CDCl_3$): δ 7.68 (d, J = 15.86 Hz, 1H, db**H**), 7.6 (d, J = 8.3 Hz, 2H, Ar**H**), 7.33 (d,, J = 15.86 Hz, 1H, db**H**), 7.23 (s, 2H, Ar**H**), 6.93 (d, J = 8.3 Hz, 2H, Ar**H**), 6.61 (s, 1H, Ar**H**), 6.56 (br s, 1H, −N**H**), 6.48 (s, 1H, Ar**H**), 6.2 (s, 2H, Ar**H**), 5.93 and 5.95 (AB q, J = 1.51 Hz, 2H, −OC**H**$_2$O−), 4.6 (s, 2H, −COC**H**$_2$O−), 4.51 (d, J = 5.28 Hz, 1H, 1-**H**), 4.36–4.44 (m, 2H, 11-**H**), 3.94 (s, 6H, OC**H**$_3$), 3.9 (s, 3H, −OCH3), 3.87 (d, J = 6.04 Hz, 1H, 4-**H**), 3.77 (s, 3H, −OCH3), 3.72 (s, 6H, −OCH3), 2.85–3.03 (m, 1H, 3-**H**), 2.66–2.77 (dd, J = 14.35, 5.28 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.92, 173.92, 167.89, 158.43, 153.01, 152.51, 148.39, 147.55, 143.62, 142.42, 137.2, 134.48, 133.32, 132.35, 130.26, 129.26, 128.08, 120.39, 115.01, 110.02, 108.79, 108.08, 106.01, 101.56, 68.64, 66.98, 60.85, 60.6, 56.29, 56.09, 47.77, 43.63, 41.53, 37.08; ESI-MS: 768 (M + H)$^+$; HRMS calcd for $C_{42}H_{42}NO_{13}$, 768.1764, found 768.1753.

*4.1.6.2. 4β-[2-{2-Methoxy-4-[(E)-3-(3-methoxyphenyl)-3-oxo-1-propenyl]phenoxy} acetamide]-4-desoxy-podophyllotoxin (**15b**).* Yellow solid, yield 67%; mp: 225–228 °C; $[\alpha]_D^{25}$ = −117.1 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69 (d, J = 15.86 Hz, 1H, db**H**), 7.55–7.59 (dd, J = 7.55, 1.51 Hz, 1H, Ar**H**), 7.49–7.52 (dd, J = 3.02, 1.51 Hz, 1H, Ar**H**), 7.33–7.42 (m, 2H, Ar**H**, db**H**), 7.23–7.3 (m, 1H, Ar**H**), 7.07–7.12 (dd, J = 8.3, 3.02 Hz, 1H, Ar**H**), 7.06 (d, J = 2.26 Hz, 1H, Ar**H**), 6.98 (d, J = 8.3 Hz, 1H, Ar**H**), 6.63 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.51 (br s, 1H, −N**H**), 6.24 (s, 2H, Ar**H**), 5.96 and 5.98 (AB q, J = 1.51 Hz, 2H, −OC**H**$_2$O−), 4.63 (s, 2H, −COC**H**$_2$O−), 4.6 (d, J = 4.53 Hz, 1H, 1-**H**), 4.34–4.42 (m, 2H, 11-**H**), 3.89 (s, 3H, −OCH3), 3.86 (d, J = 5.4 Hz, 1H, 4-**H**), 3.81 (s, 3H, −OCH3), 3.75 (s, 6H, −OCH3), 3.69 (s, 3H, −OCH3), 2.86–3.02 (m, 1H, 3-**H**), 2.75–2.83 (dd, J = 14.35, 4.53 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.97, 173.99, 168.53, 159.82, 152.59, 149.8, 148.8, 148.37, 147.58, 143.9, 139.44, 137.28, 134.52, 132.16, 130.8, 129.51, 128.58, 122.5, 121.6, 120.91, 119.06, 116.68, 112.98, 111.32, 109.96, 109.01, 108.11, 101.56, 70.11, 68.68, 60.67, 56.16, 55.64, 55.43, 47.6, 43.73, 41.69, 37.11; ESI-MS: 738 (M + H)$^+$; HRMS calcd for $C_{41}H_{40}NO_{12}$, 738.2461, found 738.2448.

*4.1.6.3. 4β-[2-{2-Methoxy-4-[(E)-3-(4-methoxyphenyl)-3-oxo-1-propenyl]phenoxy} acetamide]-4-desoxy-podophyllotoxin (**15c**).* Yellow solid, yield 67%; mp: 223–226 °C; $[\alpha]_D^{25}$ = −119.4 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.0 (d, J = 8.68 Hz, 2H, Ar**H**), 7.66 (d, J = 15.48 Hz, 1H, db**H**), 7.39 (d, J = 15.48 Hz, 1H, db**H**), 7.32 (d, J = 7.9 Hz, 1H, Ar**H**), 7.21–7.27 (m, 1H, Ar**H**), 7.05 (d, J = 2.2 Hz, 1H, Ar**H**), 6.95 (d, J = 8.63 Hz, 2H, Ar**H**), 6.55 (br s, 1H, −N**H**), 6.63 (s, 1H, Ar**H**), 6.53 (s, 1H, Ar**H**), 6.24 (s, 2H, Ar**H**), 5.95 and 5.97 (AB q, J = 1.3 Hz, 2H, −OC**H**$_2$O−), 4.63 (s, 2H, −COC**H**$_2$O−), 4.59 (d, J = 4.9 Hz, 1H, 1-**H**), 4.34–4.42 (m, 2H, 11-**H**), 3.89 (s, 3H, −OCH3), 3.87 (d, J = 5.1 Hz, 1H, 4-**H**), 3.82 (s, 3H, −OCH3), 3.74 (s, 6H, −OCH3), 3.69 (s, 3H, −OCH3), 2.86–3.03 (m, 1H, 3-**H**), 2.75–2.85 (dd, J = 14.35, 4.9 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.44, 174.03, 168.62, 163.4, 152.56, 149.73, 148.67, 148.34, 147.55, 143.02, 137.17, 134.54, 132.12, 130.97, 130.85, 130.71, 128.56, 122.22, 121.34, 116.66, 113.77, 111.37, 109.93, 109, 108.1, 101.55, 70.09, 68.68, 60.65, 56.13, 55.6, 55.41, 47.58, 43.7, 41.66, 37.08; ESI-MS: 760 (M + Na)$^+$; HRMS calcd for $C_{41}H_{39}NO_{12}Na$, 760.2345, found 760.2369.

*4.1.6.4. 4β-[2-{2-Methoxy-4-[(E)-3-(3-nitrophenyl)-3-oxo-1-propenyl]phenoxy} acetamide]-4-desoxy-podophyllotoxin (**15d**).* Yellow solid, yield 62%; mp: 260–263 °C; $[\alpha]_D^{25}$ = −115.3 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.7 (s, 1H, Ar**H**), 8.41–8.46 (dd, J = 8.3, 2.26 Hz, 1H, Ar**H**), 8.29–8.34 (dd, J = 8.3, 1.51 Hz, 1H, Ar**H**), 7.81 (d, J = 15.86 Hz, 1H, db**H**), 7.7 (t, J = 8.3, 7.75 Hz, 1H, Ar**H**), 7.35 (d, J = 15.86 Hz, 1H, db**H**), 7.2–7.24 (dd, J = 8.3, 2.26 Hz, 1H, Ar**H**), 7.15 (d, J = 1.51 Hz, 1H, Ar**H**), 6.61 (br s, 1H, −N**H**), 6.82 (d, J = 8.3 Hz, 1H, Ar**H**), 6.66 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.24 (s, 2H, Ar**H**), 5.93 and 5.95 (AB q, J = 1.51 Hz, 2H, −OC**H**$_2$O−), 4.69 (s, 2H, −COC**H**$_2$O−), 4.58 (d, J = 4.5 Hz, 1H, 1-**H**), 4.34–4.42 (m, 2H, 11-**H**), 3.97 (s, 3H, −OCH3), 3.88 (d, J = 6.04 Hz, 1H, 4-**H**), 3.77 (s, 6H, −OCH3), 3.69 (s, 3H, −OCH3), 2.84–3.02 (m, 1H, 3-**H**), 2.65–2.76 (dd, J = 14.35, 4.5 Hz, 1H, 2-**H**); ESI-MS: 753 (M + H)$^+$; HRMS calcd for $C_{40}H_{37}N_2O_{13}$, 753.1149, found 753.1157.

*4.1.6.5. 4β-[2-{2-Methoxy-4-[(E)-3-(3,4,5-trimethoxyphenyl)-3-oxo-1-propenyl]phenoxy} acetamide]-4-desoxy-podophyllotoxin (**15e**).* Yellow solid, yield 72%; mp: 248–251 °C; $[\alpha]_D^{25}$ = −121.8 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73 (d, J = 15.1 Hz, 1H, db**H**), 7.29 (d, J = 15.48 Hz, 1H, db**H**), 7.19–7.26 (m, 3H, Ar**H**), 7.13 (d, J = 1.88 Hz, 1H, Ar**H**), 6.8 (d, J = 8.3 Hz, 1H, Ar**H**), 6.71 (s, 1H, Ar**H**), 6.58 (br s, 1H, −N**H**), 6.53 (s, 1H, Ar**H**), 6.36 (s, 2H, Ar**H**), 5.94 and 5.96 (AB q, J = 1.4 Hz, 2H, −OC**H**$_2$O−), 4.63 (s, 2H, −COC**H**$_2$O−), 4.45 (d, J = 4.9 Hz, 1H, 1-**H**), 4.35–4.41 (m, 2H, 11-**H**), 3.94 (s, 6H, −OCH3), 3.93 (s, 3H, −OCH3), 3.91 (s, 3H, −OCH3), 3.87 (d, J = 6.04 Hz, 1H, 4-**H**), 3.83 (s, 3H, −OCH3), 3.81 (s, 6H, −OCH3), 2.95–3.03 (m, 1H, 3-**H**), 2.85–2.55 (dd, J = 14.35, 4.9 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.67, 178.27, 173.5, 153.86, 153.01, 149.69, 147.35, 146.85, 145.21, 142.46, 138.72, 133.82, 130.8, 130.15, 128.81, 127.9, 122.91, 119.67, 112.23, 110.58, 109.36, 106.84, 106.07, 105.1, 101.2, 69.86, 68.5, 60.76, 60.05, 56.88, 56.08, 54.62, 47.26, 43.43, 41.32, 37.04; ESI-MS: 798 (M + H)$^+$; HRMS calcd for $C_{43}H_{44}NO_{14}$, 798.2755, found 798.2761.

*4.1.6.6. 4β-[2-{2-Methoxy-4-[(E)-3-(4-fluorophenyl)-3-oxo-1-propenyl]phenoxy} acetamide]-4-desoxy-podophyllotoxin (**15f**).* Yellow solid, yield 67%; mp: 216–219 °C; $[\alpha]_D^{25}$ = −120.8 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99–8.09 (m, 2H, Ar**H**), 7.68 (d, J = 15.67 Hz, 1H, db**H**), 7.35 (d, J = 15.67 Hz, 1H, db**H**), 7.2–7.29 (m, 1H, Ar**H**), 7.18 (d, J = 8.3 Hz, 2H, Ar**H**), 7.06 (d, J = 1.51 Hz, 1H, Ar**H**), 6.98 (d, J = 8.3 Hz, 1H, Ar**H**), 6.64 (s, 1H, Ar**H**), 6.55 (br s, 1H, −N**H**), 6.53 (s, 1H, Ar**H**), 6.24 (s, 2H, Ar**H**), 5.96 and 5.98 (AB q, J = 1.32 Hz, 2H, −OC**H**$_2$O−), 4.63 (s, 2H, −COC**H**$_2$O−), 4.59 (d, J = 4.91 Hz, 1H, 1-**H**), 4.33–4.41 (m, 2H, 11-**H**), 3.91 (s, 3H, −OCH3), 3.88 (d, J = 5.4 Hz, 1H, 4-**H**), 3.74 (s, 6H, −OCH3), 3.7 (s, 3H, −OCH3), 2.86–3.02 (m, 1H, 3-**H**), 2.74–2.83 (dd, J = 13.97, 4.91 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.56, 174.02, 168.48, 152.59, 149.81, 148.93, 148.37, 147.58, 144.07, 137.34, 134.51, 132.16, 131.07, 130.94, 130.67, 128.59, 122.46, 121.09, 116.66, 115.82, 115.53, 111.42, 109.97, 109.01, 108.12, 101.56, 70.07, 68.68, 60.66, 56.16, 55.66, 47.59, 43.73, 41.69, 37.09; ESI-MS: 726 (M + H)$^+$; HRMS calcd for $C_{40}H_{37}NO_{11}$, 726.2317, found 726.2301.

*4.1.6.7. 4β-[2-{3-[(E)-3-Oxo-3-(3,4,5-trimethoxyphenyl)-1-propenyl]phenoxy} acetamide]-4-desoxy-podophyllotoxin (**15g**).* Yellow solid, yield 71%; mp: 236–237 °C; $[\alpha]_D^{25}$ = −122.7 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69 (d, J = 15.1 Hz, 1H, db**H**), 7.41 (d, J = 15.1 Hz, 1H, db**H**), 7.28–7.38 (m, 1H, Ar**H**), 7.22 (s, 2H, Ar**H**), 7.13–7.21 (m, 2H, Ar**H**), 6.91–6.98 (dd, J = 8.3, 2.26 Hz, 1H, Ar**H**), 6.61 (s, 1H, Ar**H**), 6.54 (br s, 1H, −N**H**), 6.47 (s, 1H, Ar**H**), 6.2 (s, 2H, Ar**H**), 5.94 and 5.96 (AB q, J = 1.51 Hz, 2H, −OC**H**$_2$O−), 4.61 (s, 2H, −COC**H**$_2$O−), 4.5 (d, J = 4.6 Hz, 1H, 1-**H**), 4.35–4.46 (m, 2H, 11-**H**), 3.94 (s, 6H, −OCH3), 3.91 (s, 3H, −OCH3), 3.86 (d, J = 6.06 Hz, 1H, 4-**H**), 3.77 (s, 3H, −OCH3), 3.73 (s, 6H, −OCH3), 2.83–3.03 (m, 1H, 3-**H**), 2.63–2.75 (dd, J = 14.35, 4.6 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.86, 173.94, 168.11, 157.14, 153.1, 152.56, 148.45, 147.61, 143.62, 142.7, 137.26, 136.78, 134.48, 133.06, 132.42, 130.33, 128.16, 122.67, 122.43, 116.26, 114.73, 110.07, 108.78, 108.14, 106.18, 101.61, 68.69, 67.13, 60.9, 60.64, 56.37, 56.13, 47.82, 43.67, 41.58, 37.15; ESI-MS: 790 (M + Na)$^+$; HRMS calcd for $C_{42}H_{41}NO_{13}Na$, 790.2497, found 790.2475.

*4.1.6.8. 4β-[2-{2-methoxy-5-[(E)-3-oxo-3-(3,4,5-trimethoxyphenyl)-1-propenyl]phenoxy} acetamide]-4-desoxy-podophyllotoxin (**15h**).* Yellow solid, yield 70%; mp: 245–248 °C; $[\alpha]_D^{25}$ = −120.3 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 (d, J = 15.48 Hz, 1H, db**H**),

7.29 (d, J = 15.48 Hz, 1H, db**H**), 7.19–7.26 (m, 3H, Ar**H**), 7.15 (d, J = 2.24 Hz, 1H, Ar**H**), 6.88 (d, J = 8.3 Hz, 1H, Ar**H**), 6.69 (s, 1H, Ar**H**), 6.54 (br s, 1H, −N**H**), 6.52 (s, 1H, Ar**H**), 6.23 (s, 2H, Ar**H**), 5.93 and 5.95 (AB q, J = 1.51 Hz, 2H, −OC**H**$_2$O−), 4.63 (s, 2H, −COC**H**$_2$O−), 4.58 (d, J = 4.72 Hz, 1H, 1-**H**), 4.37–4.45 (m, 2H, 11-**H**), 3.95 (s, 6H, −OCH3), 3.91 (s, 3H, −OCH3), 3.86 (d, J = 5.21 Hz, 1H, 4-**H**), 3.78 (s, 3H, −OCH3), 3.74 (s, 6H, −OCH3), 3.68 (s, 3H, −OCH3), 2.86–3.02 (m, 1H, 3-**H**), 2.74–2.83 (dd, J = 14.16, 4.72 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.89, 174.03, 168.7, 153.1, 152.61, 151.73, 148.41, 147.73, 147.27, 143.52, 142.51, 137.3, 134.51, 133.43, 132.22, 128.61, 125.55, 120.56, 116.52, 112.15, 110.02, 109.06, 108.5, 108.12, 106.09, 101.59, 70.65, 68.72, 60.93, 60.69, 56.41, 56.18, 55.7, 47.6, 43.76, 41.73, 37.14; ESI-MS: 798 $(M + H)^+$; HRMS calcd for $C_{43}H_{44}NO_{14}$, 798.2724, found 798.2741.

*4.1.7. General procedure for the synthesis of compounds **17a–h***

These compounds were synthesized according to the general method described for compounds **14a–h** by employing compound **12** (1.0 mmol) and corresponding *trans*-cinnamic acids **16a–j** (1 mmol).

*4.1.7.1. 4β-[(E)-3-Phenyl-2-propenamido]-4-desoxy-podophyllotoxin (**17a**).* Yellow solid, yield 62%; mp: 175–178 °C; $[\alpha]_D^{25}$ = −131.2 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.62 (d, J = 15.86 Hz, 1H, db**H**), 7.38–7.47 (m, 2H, Ar**H**), 7.29–7.36 (m, 3H, Ar**H**), 6.81 (s, 1H, Ar**H**), 6.46 (s, 1H, Ar**H**), 6.41 (d, J = 15.86 Hz, 1H, db**H**), 6.32 (br s, 1H, −N**H**), 6.21 (s, 2H, Ar**H**), 5.92 and 5.94 (AB q, J = 1.3 Hz, 2H, −OC**H**$_2$O−), 4.47 (d, J = 5.28 Hz, 1H, 1-**H**), 4.35–4.43 (m, 2H, 11-**H**), 3.81 (d, J = 5.21 Hz, 1H, 4-**H**), 3.74 (s, 3H, −OCH3), 3.68 (s, 6H, −OCH3), 2.89–3.01 (m, 1H, 3-**H**), 2.8–2.88 (dd, J = 14.35, 5.28 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.44, 165.9, 152.49, 148.24, 147.56, 142.42, 137, 134.83, 134.3, 132.24, 130.03, 129, 128.8, 127.78, 119.29, 109.93, 109.15, 108.05, 101.53, 69.07, 60.61, 56.08, 48.09, 43.7, 41.71, 37.38; ESI-MS: 544 $(M + H)^+$; HRMS calcd for $C_{31}H_{29}NO_8$, 544.1396, found 544.1378.

*4.1.7.2. 4β-[(E)-3-(4-Fluorophenyl)-2-propenamido]-4-desoxy-podophyllotoxin (**17b**).* Yellow solid, yield 66%; mp: 179–182 °C; $[\alpha]_D^{25}$ = −135.5 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66 (d, J = 15.86 Hz, 1H, db**H**), 7.48 (t, J = 9.06 Hz, 2H, Ar**H**), 7.07 (t, J = 9.06 Hz, 2H, Ar**H**), 6.81 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.36 (d, J = 15.86 Hz, 1H, db**H**), 6.33 (br s, 1H, −N**H**), 6.3 (s, 2H, Ar**H**), 5.95 and 5.97 (AB q, J = 1.22 Hz, 2H, −OC**H**$_2$O−), 4.61 (d, J = 4.53 Hz, 1H, 1-**H**), 4.44–4.52 (m, 2H, 11-**H**), 3.89 (d, J = 5.48 Hz, 1H, 4-**H**), 3.81 (s, 3H, −OCH3), 3.75 (s, 6H, −OCH3), 2.96–3.1 (m, 1H, 3-**H**), 2.87–2.96 (dd, J = 14.35, 4.53 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.42, 165.76, 152.55, 148.33, 147.62, 141.31, 137.09, 134.77, 132.31, 130.58, 129.73, 128.89, 118.94, 116.15, 115.86, 109.99, 109.14, 108.07, 101.59, 69.11, 60.67, 56.13, 48.21, 43.72, 41.77, 37.43; ESI-MS: 584 $(M + Na)^+$; HRMS calcd for $C_{31}H_{28}NO_8FNa$, 584.1688, found 584.1696.

*4.1.7.3. 4β-[(E)-3-(4-Chlorophenyl)-2-propenamido]-4-desoxy-podophyllotoxin (**17c**).* Yellow solid, yield 65%; mp: 175–178 °C; $[\alpha]_D^{25}$ = −134.4 (c = 0.5 in $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64 (d, J = 15.38 Hz, 1H, db**H**), 7.42 (d, J = 8.79 Hz, 2H, Ar**H**), 7.35 (d, J = 8.79 Hz, 2H, Ar**H**), 6.81 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.37 (d, J = 15.38 Hz, 1H, db**H**), 6.33 (br s, 1H, −N**H**), 6.29 (s, 2H, Ar**H**), 5.95 and 5.97 (AB q, J = 1.2 Hz, 2H, −OC**H**$_2$O−), 4.61 (d, J = 4.39 Hz, 1H, 1-**H**), 4.45–4.52 (m, 2H, 11-**H**), 3.88 (d, J = 5.2 Hz, 1H, 4-**H**), 3.8 (s, 3H, −OCH3), 3.75 (s, 6H,−OC**H**$_3$), 2.97–3.09 (m, 1H, 3-**H**), 2.88–2.95 (dd, J = 13.91, 4.39 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.46, 165.67, 152.5, 148.28, 147.58, 141.06, 136.95, 135.88, 134.81, 132.83, 132.23, 129.25, 129.09, 128.96, 119.87, 109.93, 109.13, 108.07, 101.55, 69.06, 60.62, 56.1, 48.15, 43.7, 41.72, 37.36; ESI-MS: 600 $(M + Na)^+$; HRMS calcd for $C_{31}H_{28}NO_8NaCl$, 600.1401, found 600.1386.

*4.1.7.4. 4β-[(E)-3-(4-Bromophenyl)-2-propenamido]-4-desoxy-podophyllotoxin (**17d**).* Yellow solid, yield 60%; mp: 184–187 °C; $[\alpha]_D^{25}$ = −136.8 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58 (d, J = 15.38 Hz, 1H, db**H**), 7.46 (d, J = 8.79 Hz, 2H, Ar**H**), 7.29 (d, J = 8.79 Hz, 2H, Ar**H**), 6.79 (s, 1H, Ar**H**), 6.51 (s, 1H, Ar**H**), 6.41 (d, J = 15.38 Hz, 1H, db**H**), 6.32 (br s, 1H, −N**H**), 6.26 (s, 2H, Ar**H**), 5.93 and 5.95 (AB q, J = 1.3 Hz, 2H, −OC**H**$_2$O−), 4.52 (d, J = 3.66 Hz, 1H, 1-**H**), 4.4–4.49 (m, 2H, 11-**H**), 3.84 (d, J = 5.54 Hz, 1H, 4-**H**), 3.74 (s, 3H, −OCH3), 3.69 (s, 6H, −OCH3), 2.93–3.06 (m, 2H, 3-**H**), 2.81–2.89 (dd, J = 14.1, 3.66 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.46, 165.61, 152.43, 148.22, 147.51, 141, 136.85, 134.85, 133.22, 132.14, 132.01, 129.14, 128.87, 124.16, 120, 109.86, 109.12, 107.96, 101.53, 69, 60.58, 50.04, 48.06, 43.65, 41.64, 37.3; ESI-MS: 622 $(M)^+$; HRMS calcd for $C_{31}H_{28}NO_8Br$, 622.0891, found 622.0895.

*4.1.7.5. 4β-[(E)-3-(4-Methoxyphenyl)-2-propenamido]-4-desoxy-podophyllotoxin (**17e**).* Yellow solid, yield 63%; mp: 187–190 °C; $[\alpha]_D^{25}$ = −138.6 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.65 (d, J = 15.1 Hz, 1H, db**H**), 7.44 (d, J = 8.3 Hz, 2H, Ar**H**), 6.9 (d, J = 8.3 Hz, 2H, Ar**H**), 6.81 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.37 (br s, 1H, −N**H**), 6.3 (s, 2H, Ar**H**), 6.26 (d, J = 15.1 Hz, 1H, db**H**), 5.94 and 5.96 (AB q, J = 1.51 Hz, 2H, −OC**H**$_2$O−), 4.61 (d, J = 4.53 Hz, 1H, 1-**H**), 4.43–4.52 (m, 2H, 11-**H**), 3.89 (d, J = 5.1 Hz, 1H, 4-**H**), 3.84 (s, 3H, −OCH3), 3.81 (s, 3H, −OCH3), 3.75 (s, 6H, −OCH3), 2.96–3.08 (m, 1H, 3-**H**), 2.87–2.95 (dd, J = 14.35, 4.53 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.47, 166.29, 161.18, 152.53, 148.27, 147.58, 142.2, 137.07, 134.81, 132.29, 129.46, 129.05, 126.98, 116.68, 114.28, 109.96, 109.97, 108.07, 101.55, 69.15, 60.66, 56.13, 55.3, 48.12, 43.73, 41.76, 37.47; ESI-MS: 596 $(M + Na)^+$; HRMS calcd for $C_{32}H_{31}NO_9Na$, 596.1896, found 596.1806.

*4.1.7.6. 4β-[(E)-3-(4-Trifluoromethylphenyl)-2-propenamido]-4-desoxy-podophyllotoxin (**17f**).* Yellow solid, yield 68%; mp: 196–199 °C; $[\alpha]_D^{25}$ = −138.1 (c = 0.5 in $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.71 (d, J = 15.86 Hz, 1H, db**H**), 7.65 (d, J = 9.06 Hz, 2H, Ar**H**), 7.59 (d, J = 8.3 Hz, 2H, Ar**H**), 6.82 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.48 (d, J = 15.86 Hz, 1H, db**H**), 6.39 (br s, 1H, −N**H**), 6.30 (s, 2H, Ar**H**), 5.96 and 5.98 (AB q, J = 1.51 Hz, 2H, −OC**H**$_2$O−), 4.61 (d, J = 5.28 Hz, 1H, 1-**H**), 4.44–4.53 (m, 2H, 11-**H**), 3.89 (d, J = 5.1 Hz, 1H, 4-**H**), 3.81 (s, 3H, −OCH3), 3.75 (s, 6H, −OCH3), 2.97–3.13 (m, 1H, 3-**H**), 2.88–2.96 (dd, J = 14.35, 5.28 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.42, 165.29, 152.51, 148.33, 147.6, 140.63, 137.78, 137.02, 134.8, 132.24, 131.68, 131.28, 128.81, 127.92, 125.8, 121.88, 109.93, 109.12, 108.07, 101.56, 69.01, 60.61, 56.09, 48.2, 43.7, 41.72, 37.34; ESI-MS: 634 $(M + Na)^+$; HRMS calcd for $C_{32}H_{28}NO_8F_3Na$, 634.1657, found 634.1644.

*4.1.7.7. 4β-[(E)-3-(4-Nitrophenyl)-2-propenamido]-4-desoxy-podophyllotoxin (**17g**).* Yellow solid, yield 65%; mp: 197–199 °C; $[\alpha]_D^{25}$ = −134.7 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.25 (d, J = 8.3 Hz, 2H, Ar**H**), 7.74 (d, J = 15.1 Hz, 1H, db**H**), 7.63 (d, J = 8.3 Hz, 2H, Ar**H**), 6.81 (s, 1H, Ar**H**), 6.55 (s, 1H, Ar**H**), 6.53 (d, J = 15.1 Hz, 1H, db**H**), 6.4 (br s, 1H, −N**H**), 6.3 (s, 2H, Ar**H**), 5.96 and 5.98 (AB q, J = 1.4 Hz, 2H, −OC**H**$_2$O−), 4.62 (d, J = 4.53 Hz, 1H, 1-**H**), 4.44–4.53 (m, 2H, 11-**H**), 3.88 (d, J = 5.8 Hz, 1H, 4-**H**), 3.8 (s, 3H, −OCH3), 3.75 (s, 6H, −OCH3), 2.97–3.12 (m, 1H, 3-**H**), 2.86–2.96 (dd, J = 14.35, 4.53 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.35, 164.78, 152.53, 148.4, 148.2, 147.64, 140.65, 139.64, 137.02, 134.79, 132.29, 128.64, 128.39, 124.13, 123.62, 110, 109.11, 108.08, 101.63, 69.01, 60.64, 56.14, 48.33, 43.7, 41.72, 37.35; ESI-MS: 611 $(M + Na)^+$; HRMS calcd for $C_{31}H_{28}N_2O_{10}Na$, 611.1661, found 611.1641.

*4.1.7.8. 4β-[(E)-3-(3,4-Dichlorophenyl)-2-propenamido]-4-desoxy-podophyllotoxin (**17h**).* Yellow solid, yield 67%; mp: 181–183 °C; $[\alpha]_D^{25}$ = −131.5 (c = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$):

δ 7.55–7.63 (m, 2H, Ar**H**, db**H**), 7.46 (d, *J* = 8.3 Hz, 1H, Ar**H**), 7.28–7.33 (dd, *J* = 8.3, 2.26 Hz, 1H, Ar**H**), 6.8 (s, 1H, Ar**H**), 6.54 (s, 1H, Ar**H**), 6.39 (d, *J* = 15.86 Hz, 1H, db**H**), 6.35 (br s, 1H, −N**H**), 6.29 (s, 2H, Ar**H**), 5.97 and 5.99 (AB q, *J* = 1.6 Hz, 2H, −OC**H**$_2$O−), 4.61 (d, *J* = 4.53 Hz, 1H, 1-**H**), 4.43–4.51 (m, 2H, 11-**H**), 3.87 (d, *J* = 5.21 Hz, 1H, 4-**H**), 3.8 (s, 3H, −OCH3), 3.75 (s, 6H, −OCH3), 2.96–3.12 (m, 1H, 3-**H**), 2.86–2.95 (dd, *J* = 14.35, 4.53 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.39, 165.19, 152.5, 148.33, 147.61, 139.8, 139.99, 134.8, 134.42, 133.89, 133.1, 132.24, 130.83, 129.11, 128.78, 126.98, 121.16, 109.95, 109.1, 108.08, 101.58, 69.01, 60.61, 56.12, 48.21, 43.69, 41.71, 37.34; ESI-MS: 613 $(M + H)^+$; HRMS calcd for $C_{31}H_{28}Cl_2NO_8$, 613.1461, found 613.1442.

*4.1.7.9. 4β-[(E)-3-(3,4,5-Trimethoxyphenyl)-2-propenamido]-4-desoxy-podophyllotoxin (**17i**).* Yellow solid, yield 62%; mp: 199–202 °C; $[\alpha]_D^{25} = -137.2$ (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 (d, *J* = 15.8 Hz, 1H, db**H**), 7.23 (s, 2H, Ar**H**), 6.8 (s, 1H, Ar**H**), 6.53 (s, 1H, Ar**H**), 6.35 (d, *J* = 15.18 Hz, 1H, db**H**), 6.33 (br s, 1H, −N**H**), 6.31 (s, 2H, Ar**H**), 5.96 and 5.98 (AB q, *J* = 1.5 Hz, 2H, −OC**H**$_2$O−), 4.61 (d, *J* = 4.5 Hz, 1H, 1-**H**), 4.42–4.52 (m, 2H, 11-**H**), 3.9 (d, *J* = 5.4 Hz, 1H, 4-**H**), 3.87 (s, 6H, −OCH3), 3.8 (s, 3H, −OCH3), 3.77 (s, 3H, −OCH3), 3.73 (s, 6H, −OCH3), 2.97–3.09 (m, 1H, 3-**H**), 2.87–2.96 (dd, *J* = 14.3, 4.5 Hz, 1H, 2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.38, 165.86, 153.34, 152.53, 148.3, 147.55, 142.46, 139.8, 137.13, 134.72, 132.32, 129.94, 128.88, 118.64, 109.96, 109.08, 108.11, 105.07, 101.53, 69.1, 60.86, 60.65, 56.14, 56.04, 48.2, 43.71, 41.75, 37.44; ESI-MS: 634 $(M + H)^+$; HRMS calcd for $C_{34}H_{36}NO_{11}$, 634.1648.1642, found 634.1625.

*4.1.8. General procedure for the synthesis [39] of compounds **19a**,**b***

To a solution of compound **18** (1.0 mmol) and 2,4-pentanedione in acetonitrile (20 ml) was added 1 ml of 1N HCl solution and the reaction mixture was stirred at room temperature for 24 h. The reaction was monitored by TLC. After completion of reaction neutralize with saturated sodium bicarbonate solution and extracted with ethyl acetate (2 × 30 ml). The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography on silica gel using ethyl acetate and hexane as solvent system to obtain the pure products as solids.

*4.1.8.1. 3-Acetyl-2,4-dimethylquinoline (**19a**).* Liquid, yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.3 Hz, 1H, Ar**H**), 7.95 (d, *J* = 8.3 Hz, 1H, Ar**H**), 7.66–7.73 (m, 1H, Ar**H**), 7.49–7.57 (m, 1H, Ar**H**), 2.63 (s, 3H, −COC**H**$_3$), 2.58 (s, 3H, −C**H**$_3$), 2.56 (s, 3H, −C**H**$_3$); ESI-MS: 200 $(M + H)^+$.

*4.1.8.2. 3-Acetyl-2-methyl-4-phenylquinoline (**19b**).* White solid, yield 75%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.3 Hz, 1H, Ar**H**), 7.64–7.72 (m, 1H, Ar**H**), 7.56–7.62 (dd, *J* = 8.3, 1.51 Hz, 1H, Ar**H**), 7.47–7.54 (m, 3H, Ar**H**), 7.39–7.44 (dd, *J* = 8.3, 1.51 Hz, 1H, Ar**H**), 7.32–7.38 (m, 2H, Ar**H**), 2.67 (s, 3H, −COC**H**$_3$), 1.96 (s, 3H, −C**H**$_3$); ESI-MS: 262 $(M + H)^+$.

*4.1.9. General procedure for the synthesis of compounds **20a**,**b***

To a stirred mixture of acetylquinolines **19a**,**b** (1 mmol) and vanillin (1 mmol) in ethanol (10 ml) was added 50% aqueous solution of potassium hydroxide (1 ml) and stirred for 12 h at reflux temperature. After completion of the reaction checked by TLC, the solvent was evaporated, neutralized with 1N HCl solution and extracted with ethyl acetate (2 × 50 ml). The combined organic fractions were washed with water followed by brine, dried over Na_2SO_4 and purified by column chromatography on silica gel using ethyl acetate and hexane to afford yellow solid.

*4.1.9.1. (E)-1-(2,4-dimethyl-3-quinolyl)-3-(4-hydroxy-3-methoxyphenyl)-2-propen-1-one (**20a**).* Yellow solid, yield 85%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99–8.12 (m, 2H, Ar**H**), 7.7–7.8 (m, 1H, Ar**H**), 7.53–7.64 (m, 1H, Ar**H**), 7.08 (d, *J* = 16.23 Hz, 1H, db**H**), 6.98–7.04 (m, 2H, Ar**H**), 6.94 (d, *J* = 16.15 Hz, 1H, db**H**), 6.9 (d, *J* = 8.11 Hz, 1H, Ar**H**), 5.92 (br s, 1H, ArO**H**), 3.89 (s, 3H, −OCH3), 2.63 (s, 3H, −C**H**$_3$), 2.59 (s, 3H, −C**H**$_3$); ESI-MS: 334 $(M + H)^+$.

*4.1.9.2. (E)-3-(4-hydroxy-3-methoxyphenyl)-1-(2-methyl-4-phenyl-3-quinolyl)-2-propen-1-one (**20b**)*

Yellow solid, yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.3 Hz, 1H, Ar**H**), 7.67–7.75 (m, 1H, Ar**H**), 7.56–7.62 (dd, *J* = 8.3, 1.51 Hz, 1H, Ar**H**), 7.41–7.47 (m, 1H, Ar**H**), 7.34–7.39 (m, 3H, Ar**H**), 7.27–7.33 (m, 2H, Ar**H**), 6.96 (d, *J* = 15.86 Hz, 1H, db**H**), 6.77–6.87 (m, 3H, Ar**H**), 6.41 (d, *J* = 15.86 Hz, 1H, db**H**), 5.97 (br s, 1H, ArO**H**), 3.87 (s, 3H, −OCH3), 2.69 (s, 3H, −C**H**$_3$); ESI-MS: 396 $(M + H)^+$.

*4.1.10. General procedure for the synthesis of compounds **21a**,**b***

These compounds synthesized according to method described for compounds **10a**–**h** by employing compound **20a**,**b** (1.0 mmol), and α-bromoethylacetate (1.2 mmol) to obtain the pure product as solid.

*4.1.10.1. Ethyl 2-{4-[(E)-3-(2,4-dimethyl-3-quinolyl)-3-oxo-1-propenyl]-2-methoxyphenoxy}acetate (**21a**).* Yellow solid, yield 80%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.07 Hz, 1H, Ar**H**), 7.98 (d, *J* = 8.07 Hz, 1H, Ar**H**), 7.67–7.73 (m, 1H, Ar**H**), 7.53 (t, *J* = 8.07, 7.06 Hz, 1H, Ar**H**), 7.05 (d, *J* = 16.15 Hz, 1H, db**H**), 6.98–7.03 (m, 2H, Ar**H**), 6.88 (d, *J* = 16.15 Hz, 1H, db**H**), 6.74 (d, *J* = 8.07 Hz, 1H, Ar**H**), 4.65 (s, 2H, −OC**H**$_2$CO−), 4.19–4.26 (q, 2H, −OC**H**$_2$−), 3.89 (s, 3H, −OCH3), 2.6 (s, 3H, Ar-C**H**$_3$), 2.56 (s, 3H, Ar-C**H**$_3$), 1.28 (t, *J* = 7.06 Hz, 3H, −C**H**$_3$); ESI-MS: 420 $(M + H)^+$.

*4.1.10.2. Ethyl 2-{2-methoxy-4-[(E)-3-(2-methyl-4-phenyl-3-quinolyl)-3-oxo-1-propenyl]phenoxy} acetate (**21b**).* Yellow solid, yield 82%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.07 Hz, 1H, Ar**H**), 7.71 (t, *J* = 8.07, 7.06 Hz, 1H, Ar**H**), 7.57–7.61 (dd, *J* = 8.3, 1.51 Hz, 1H, Ar**H**), 7.4–7.45 (m, 1H, Ar**H**), 7.34–7.39 (m, 3H, Ar**H**), 7.27–7.31 (m, 2H, Ar**H**), 6.98 (d, *J* = 16.15 Hz, 1H, db**H**), 6.8–6.86 (m, 2H, Ar**H**), 6.68 (d, *J* = 8.07 Hz, 1H, Ar**H**), 6.43 (d, *J* = 16.15 Hz, 1H, db**H**), 4.62 (s, 2H, −OC**H**$_2$CO−), 4.19–4.26 (q, 2H, −OC**H**$_2$−), 3.83 (s, 3H, −OCH3), 2.69 (s, 3H, Ar-C**H**$_3$), 1.28 (t, *J* = 7.06 Hz, 3H, −C**H**$_3$); ESI-MS: 482 $(M + H)^+$.

*4.1.11. General procedure for the synthesis of compounds **22a**,**b***

These compounds synthesized according to method described for compounds **11a**–**h** by employing compound **21a**,**b** (1 mmol), and LiOH.H_2O (3 mmol) to obtain the pure product as solid.

*4.1.11.1. 2-{4-[(E)-3-(2,4-dimethyl-3-quinolyl)-3-oxo-1-propenyl]-2-methoxyphenoxy}acetic acid (**22a**).* Yellow solid, yield 71%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.07 Hz, 1H, Ar**H**), 7.96 (br s, 1H, −COO**H**), 7.99 (d, *J* = 8.07 Hz, 1H, Ar**H**), 7.66–7.72 (m, 1H, Ar**H**), 7.53 (t, *J* = 8.07, 7.06 Hz, 1H, Ar**H**), 7.06 (d, *J* = 16.15 Hz, 1H, db**H**), 7–7.05 (m, 2H, Ar**H**), 6.9 (d, *J* = 16.15 Hz, 1H, db**H**), 6.74 (d, *J* = 8.07 Hz, 1H, Ar**H**), 4.67 (s, 2H, −OC**H**$_2$CO−), 3.9 (s, 3H, −OCH3), 2.6 (s, 3H, −C**H**$_3$), 2.56 (s, 3H, −C**H**$_3$); ESI-MS: 392 $(M + H)^+$.

*4.1.11.2. 2-{2-methoxy-4-[(E)-3-(2-methyl-4-phenyl-3-quinolyl)-3-oxo-1-propenyl] phenoxy}acetic acid (**22b**).* Yellow solid, yield 65%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.07 Hz, 1H, Ar**H**), 7.97 (bs, 1H, −COO**H**), 7.71 (t, *J* = 8.07, 7.06 Hz, 1H, Ar**H**), 7.58–7.63 (dd, *J* = 8.3, 1.51 Hz, 1H, Ar**H**), 7.42–7.45 (m, 1H, Ar**H**), 7.35–7.4 (m, 3H, Ar**H**), 7.26–7.31 (m, 2H, Ar**H**), 6.99 (d, *J* = 16.15 Hz, 1H, db**H**), 6.82–6.87 (m, 2H, Ar**H**), 6.69 (d, *J* = 8.07 Hz, 1H, Ar**H**), 6.44 (d, *J* = 16.15 Hz, 1H, db**H**), 4.66 (s, 2H, −OC**H**$_2$CO−), 3.84 (s, 3H, −OCH3), 2.67 (s, 3H, −C**H**$_3$); ESI-MS: 454 $(M + H)^+$.

*4.1.12. General procedure for the synthesis of compounds **23a**,**b***

These compounds synthesized according to method described for compounds **15a**–**h** by employing compound **22a**,**b** (1 mmol) and compound **12**(1 mmol) to obtain the pure product as solid.

*4.1.12.1. 4β-[2-{4-[(E)-3-(2,4-Dimethyl-3-quinolyl)-3-oxo-1-propenyl]-2-methoxyphenoxy} acetamide]-4-desoxy-podophyllotoxin (**23a**).* Yellow solid, yield 78%; mp: 267–270 °C; $[\alpha]_D^{25} = -154.9$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, $J = 8.3$ Hz, 1H, Ar**H**), 8.0 (d, $J = 8.12$ Hz, 1H, Ar**H**), 7.69–7.77 (m, 1H, Ar**H**), 7.55 (t, $J = 7.93$, 7.17 Hz, 1H, Ar**H**), 7.19 (d, $J = 7.36$ Hz, 1H, Ar**H**), 7.08–7.13 (dd, $J = 8.49$, 1.52 Hz, 1H, Ar**H**), 7.04 (d, $J = 16.43$ Hz, 1H, db**H**), 7.87–6.97 (m, 2H, Ar**H**, db**H**), 6.6 (s, 1H, Ar**H**), 6.52 (s, 1H, Ar**H**), 6.45 (br s, 1H, −N**H**), 6.22 (s, 2H, Ar**H**), 5.93 and 5.95 (AB q, $J = 1.51$ Hz, 2H, −OC**H**$_2$O−), 4.6 (s, 2H, −OC**H**$_2$CO−), 4.57 (d, $J = 4.72$ Hz, 1H, 1-**H**), 4.32–4.42 (m, 2H, 11-**H**), 3.92 (d, $J = 5.6$ Hz, 1H, 4-**H**), 3.78 (s, 3H, −OCH3), 3.74 (s, 6H, −OCH3), 3.62 (s, 3H, −OCH3), 2.84–3.01 (m, 1H, 3-**H**), 2.67–2.76 (dd, $J = 14.16$, 4.72 Hz, 1H, 2-**H**), 2.61 (s, 3H, −C**H**$_3$), 2.58 (s, 3H, −C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.82, 173.94, 168.36, 154.32, 152.59, 149.87, 149.44, 148.39, 147.57, 147.1, 146.88, 140.94, 137.31, 134.48, 132.97, 132.23, 129.98, 129.69, 129.02, 128.48, 127.62, 126.42, 126.02, 123.75, 122.89, 116.56, 111.33, 110.02, 109.01, 108.14, 101.55, 69.98, 68.68, 60.66, 56.16, 55.6, 47.65, 43.71, 41.66, 37.11, 23.55, 15.59; ESI-MS: 787 $(M + H)^+$; HRMS calcd for $C_{45}H_{43}N_2O_{11}$, 787.2865, found 787.2866.

*4.1.12.2. 4β-[2-{2-Methoxy-4-[(E)-3-(2-methyl-4-phenyl-3-quinolyl)-3-oxo-1-propenyl] phenoxy}acetamide]-4-desoxy-podophyllotoxin (**23b**).* Yellow solid, yield 71%; mp: 284–286 °C; $[\alpha]_D^{25} = -151.3$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, $J = 8.3$ Hz 1H, Ar**H**), 7.69–7.77 (m, 1H, Ar**H**), 7.57–7.63 (dd, $J = 8.3$, 1.51 Hz, 1H, Ar**H**), 7.41–7.48 (m, 1H, Ar**H**), 7.34–7.4 (m, 3H, Ar**H**), 7.27–7.33 (m, 2H, Ar**H**), 7.23 (d, $J = 7.55$ Hz, 1H, Ar**H**), 6.97 (d, $J = 15.86$ Hz, 1H, db**H**), 6.87–6.9 (m, 1H, Ar**H**), 6.75 (d, $J = 1.51$ Hz, 1H, Ar**H**), 6.59 (s, 1H, Ar**H**), 6.52 (s, 1H, Ar**H**), 6.44 (d, $J = 15.86$ Hz, 1H, db**H**), 6.46 (br s, 1H, −N**H**), 6.22 (s, 2H, Ar**H**), 5.94 and 5.96 (AB q, $J = 1.62$ Hz, 2H, −OC**H**$_2$O−), 4.63 (s, 2H, −OC**H**$_2$CO−), 4.54 (d, $J = 5.28$ Hz, 1H, 1-**H**), 4.33–4.48 (m, 2H, 11-**H**), 3.94 (d, $J = 5.1$ Hz, 1H, 4-**H**), 3.78 (s, 3H, −OCH3), 3.74 (s, 6H, −OCH3), 3.57 (s, 3H, −OCH3), 2.84–3.03 (m, 1H, 3-**H**), 2.7–2.78 (dd, 1H, $J = 14.35$, 5.28 Hz, 2-**H**), 2.69 (s, 3H, -C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.24, 173.94, 168.24, 154.8, 152.6, 149.77, 149.17, 148.38, 147.56, 147.04, 145.79, 145.51, 137.32, 135.09, 134.48, 132.42, 132.2, 130.2, 129.95, 129.87, 128.65, 128.52, 128.29, 127.38, 126.54, 126.27, 125.25, 122.62, 116.59, 110.9, 109.91, 108.99, 108.15, 101.54, 70.04, 68.66, 60.66, 56.17, 55.51, 47.61, 43.71, 41.68, 37.09, 23.77; ESI-MS: 849 $(M + H)^+$; HRMS calcd for $C_{50}H_{45}N_2O_{11}$, 849.2986, found 849.3023.

*4.1.13. General procedure for the synthesis of compounds **24a**,**b***

These compounds synthesized according to method described for compounds **14a**–**h** by employing compound **20a**,**b** (1 mmol), and compound **13** (1 mmol) to obtain the pure product as solid.

*4.1.13.1. 4β-[6-{4-[(E)-3-(2,4-Dimethyl-3-quinolyl)-3-oxo-1-propenyl]-2-methoxyphenoxy}hexanamido]-4-desoxy-podophyllotoxin (**24a**).* Yellow solid, yield 69%; mp: 274–277 °C; $[\alpha]_D^{25} = -145.4$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, $J = 8.32$ Hz, 1H, Ar**H**), 8.03 (d, $J = 8.32$ Hz, 1H, Ar**H**), 7.76 (t, $J = 8.32$, 7.28 Hz, 1H, Ar**H**), 7.6 (t, $J = 8.32$, 7.28 Hz, 1H, Ar**H**), 7.07 (d, $J = 15.61$ Hz, 1H, db**H**), 6.98–7.05 (m, 2H, Ar**H**), 6.94 (d, $J = 15.61$ Hz, 1H, db**H**), 6.84 (d, $J = 8.32$ Hz, 1H, Ar**H**), 6.73 (s, 1H, Ar**H**), 6.53 (s, 1H, Ar**H**), 6.36 (s, 2H, Ar**H**), 6.2 (br s, 1H, −N**H**), 5.93 and 5.95 (AB q, $J = 1.4$ Hz, 2H, −OC**H**$_2$O−), 4.58 (d, $J = 4.82$ Hz, 1H, 1-**H**), 4.29–4.41 (m, 2H, 11-**H**), 4.04 (t, $J = 6.24$ Hz, 2H, −C**H**$_2$O−), 3.91 (s, 3H, −OCH3), 3.87 (d, $J = 5.1$ Hz, 1H, 4-**H**), 3.83 (s, 3H, −OCH3), 3.8 (s, 6H, −OCH3), 3.37–3.32(dd, $J = 9.37$, 4.82 Hz, 1H, 2-**H**), 3.16–3.24 (m, 1H, 3-**H**), 2.64 (s, 3H, −C**H**$_3$), 2.59 (s, 3H, −C**H**$_3$), 2.26 (t, $J = 7.28$ Hz, 2H, −C**H**$_2$CO−), 1.83–1.91 (m, 2H, −C**H**$_2$−), 1.67–1.77 (m, 2H, −C**H**$_2$−), 1.46–1.55 (m, 2H, −C**H**$_2$−); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.15, 174.06, 168.65, 154.54, 152.17, 149.94, 149.24, 148.68, 147.78, 147.23, 146.74, 141.12, 137.38, 134.25, 132.75, 132.14, 130.15, 129.43, 129.08, 128.4, 127.65, 126.79, 126.15, 123.64, 122.81, 116.5, 111.57, 110.24, 109.28, 108.24, 101.4, 68.87, 67.46, 60.51, 56.36, 55.78, 47.49, 43.35, 42.06, 37.51, 28.55, 29.96, 25.41, 25.2, 23.41; ESI-MS: 843 $(M + H)^+$; HRMS calcd for $C_{49}H_{51}N_2O_{11}$, 843.2471, found 843.2462.

*4.1.13.2. 4β-[6-{2-Methoxy-4-[(E)-3-(2-methyl-4-phenyl-3-quinolyl)-3-oxo-1-propenyl] phenoxy}hexanamido]-4-desoxy-podophyllotoxin (**24b**).* Yellow solid, yield 65%; mp: 287–290 °C; $[\alpha]_D^{25} = -141.8$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, $J = 7.89$ Hz, 1H, Ar**H**), 7.67–7.73 (m, 1H, Ar**H**), 7.56–7.60 (dd, $J = 7.83$, 1.51 Hz, 1H, Ar**H**), 7.39–7.44 (m, 1H, Ar**H**), 7.31–7.39 (m, 3H, Ar**H**), 7.27–7.31 (m, 2H, Ar**H**), 7.22 (d, $J = 7.83$ Hz, 1H, Ar**H**), 6.96 (d, $J = 15.67$ Hz, 1H, db**H**), 6.81–6.85 (m, 1H, Ar**H**), 6.77 (d, $J = 1.51$ Hz, 1H, Ar**H**), 6.67 (s, 1H, Ar**H**), 6.47 (s, 1H, Ar**H**), 6.41 (d, $J = 15.67$ Hz, 1H, db**H**), 6.31 (s, 2H, Ar**H**), 6.15 (br s, 1H, −N**H**), 5.91 and 5.94 (AB q, $J = 1.51$ Hz, 2H, −OC**H**$_2$O−), 4.56 (d, $J = 4.21$ Hz, 1H, 1-**H**), 4.21–4.38 (m, 2H, 11-**H**), 4.1 (t, $J = 6.85$ Hz, 2H, −C**H**$_2$O−), 3.91 (s, 3H, −OCH3), 3.89 (d, $J = 5.8$ Hz, 1H, 4-**H**), 3.79 (s, 6H, −OCH3), 3.76 (s, 3H, −OCH3), 3.14–3.18(dd, $J = 9.79$, 4.56 Hz, 1H, 2-**H**), 3.06–3.14 (m, 1H, 3-**H**), 2.68 (s, 3H, −C**H**$_3$), 2.22 (t, $J = 7.83$, 6.85 Hz, 2H, −C**H**$_2$CO−), 1.79–1.87 (m, 2H, −C**H**$_2$−), 1.65–1.75 (m, 2H, −C**H**$_2$−), 1.46–1.55 (m, 2H, −C**H**$_2$−); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.68, 173.48, 168.55, 154.56, 152.02, 149.95, 149.21, 148.3, 147.64, 147.09, 145.97, 145.13, 137.35, 135.57, 134.79, 132.64, 132.24, 130.68, 129.61, 129.16, 128.46, 128.12, 127.89, 127.28, 126.85, 126.13, 125.68, 122.82, 116.47, 110.87, 109.84, 108.87, 108.09, 101.5, 69.94, 68.48, 60.6, 56.35, 55.48, 47.56, 43.87, 41.34, 37.25, 28.71, 26.75, 25.42, 25.35, 23.41; ESI-MS: 906 $(M + H)^+$; HRMS calcd for $C_{54}H_{53}N_2O_{11}$, 906.1016, found 906.1029.

4.2. Evaluation of in vitro anti-cancer activity

The cytotoxic activity of the compounds was determined using MTT assay [40]. 1×10^4 cells/well were seeded in 200 μl DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 h at 37 °C in a CO_2 incubator. Compounds, diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 h of incubation, 10 μl MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (5 mg/ml) was added to each well and the plates were further incubated for 4 h. Then the supernatant from each well was carefully removed, formazon crystals were dissolved in 100 μl of DMSO and absorbance at 540 nm wavelength was recorded.

4.3. Hoechst staining for morphological analysis of apoptosis

Cells were seeded at a density of 10,000 cells over 18-mm cover slips and incubated for 24 h. Then, the medium was replaced, and cells were treated with **17a** and **17f** at 2 μM and 5 μM for 24 h. Cells treated with vehicle (0.001% DMSO) were included as controls for all experiments. After 24 h treatment, Hoechst 33258 (Sigma–Aldrich) staining was added to the medium at a concentration of 0.5 mg/ml. After incubation for 30 min at 37 °C, cells from each dish were captured from randomly selected fields under fluorescent microscope (Leica, Germany) to qualitatively determine the proportion of viable and apoptotic cells based on their relative fluorescence and nuclear fragmentation [41].

4.4. DNA fragmentation assay

Cells were seeded (1×10^6) in six-well plates. After incubation of 24 h cells were treated with compounds **17a** and **17f** at 5 μM/ml concentration. After 48 h of treatment, cells were collected and centrifuged at 2500 rpm for 5 min at 4 °C. Pellet was collected and washed with Phosphate buffered saline (PBS). Then added 100 μl of Lysis buffer centrifuged at 3000 rpm for 5 min at 4 °C and collected supernant. And added 10 μl of 10% SDS and 10 μl of (50 mg/ml) RNase-A and incubated for 2 h at 56 °C. After incubation Proteinase K (25 mg/ml) was added and further incubated at 37 °C for 2 h. Then added 65 μl of 10 M Ammonium acetate and 500 μl of ice cold ethanol and mixed well. And these samples were incubated at −80 °C for 1 h. After incubatation samples were centrifuged at 12000 rpm for 20 min at 4 °C. After centrifuge pellet was washed with 80% ethanol and air dried for 10 min at room temperature. Dissolved the pellet in 50 μl of TE buffer and DNA laddering was determined by using 2% agarose gel electrophoresis in TE Buffer [42].

4.5. Cell cycle analysis

To determine the effect of compounds on the stages of cell cycle, A-549 cells (1 × 106) were seeded in six-well plates and treated with compounds **17a** and **17f** at concentrations of 1 and 5 μM/ml for 48 h. After 48 h treatment, both floating and trypsinized adherent cells were collected and fixed with 70% ethanol. After fixation cells were washed with PBS and stained with 50 mg/ml propidium iodide in hypotonic lysis buffer (0.1% sodium citrate, 0.1% Triton X-100) containing DNase-free RNase-A for 20 min. Stained cells were analyzed using fluorescence-activated cell sorter caliber (Becton Dickinson) [43].

4.6. Caspase-3

To determine the caspase-3 activity of the active compounds AFC conjugated Ac-DEVD substrate was used. Lung cancer cells (A-549) were seeded in 6 well plates with the confluence of 2.5×10^5 per well and are treated with the compounds at 2 μM concentration along with standard etoposide. After incubation for 24 h cell were washed with PBS and then cells were scraped in to the PBS and centrifuged at 2000 rpm for 10 min at 4 °C. Pellet was resuspended in 80 μl of lysis buffer, pellet was passed through insulin syringe followed by incubation of suspension on ice for 20–30 min centrifuged the lysate at 13,200 rpm for 20 min at 4 °C and transferred the supernatant to fresh tubes. In a 96 well black polystyrene plate, 50 μl of 2X assay buffer, 50 μl cell lysate and 2 μl of caspase-3 substrate were taken. The reaction was allowed to take place for 1 h. The fluorescence generated by the release of the fluorogenic group AFC on cleavage by caspase-3 was measured by excitation at 400 nm and emission at 505 nm for every 5 min over 1 h. Protein was estimated by Bradford's method and normalized accordingly [33b,44,45].

Acknowledgments

The authors A. M. R and N. S. R are thankful to CSIR, India and P. S is Thankful to UGC, India for the award of research fellowships.

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