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Design, synthesis, anti-inflammatory, cytotoxic and cell based studies of some novel side chain analogues of myrrhanones A & B isolated from the gum resin of *Commiphora mukul*

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ABSTRACT

Myrrhanones A (**1**) and B (**2**), isolated from the gum resin of *Commiphora mukul*, were reported to exhibit anticancer and anti-inflammatory activities. In view of their interesting skeletal features and biological activities they have been chemically modified by exploiting their side chain functionalities to synthesise 29 diverse analogues. All the synthesized analogues were screened for their cytotoxic potential against a panel of five human cancer cell lines which include DU145 (Prostate), HT-29 (Colon), MCF-7 (Breast), Hela (Cervical) and U87MG (Glioblastoma) along with a normal cell line (L132). The synthesized analogues were also screened for anti-inflammatory activity against TNF-α and IL-1β using LPS induced inflammation model employing U937 cells. The biological screening results revealed that compounds **4b** (piperidine analogue), **9d** (linear aliphatic four member amide analogue) and **9i** (*N*-methyl piperazine analogue) displayed significant cytotoxic activity against MCF-7, HT-29 and DU145 [IC_{50} (μM): 4.65 ± 1.28, 5.48 ± 0.13 and 6.63 ± 1.39] respectively. These analogues were further taken up for apoptotic assay, which confirmed that compounds **4b**, **9d** and **9i** induced apoptosis in MCF-7, HT-29, DU145 cells and arrested in G0/G1 phase. Further, compounds **9c** and **9g** found to exhibit good anti-inflammatory activity against TNF-α with IC_{50} (μM) values of 10.02 ± 2.13 and 10.53 ± 0.48 respectively, while compound **2** exhibited strong inhibitory activity against both TNF-α (IC_{50}: 9.39 ± 0.44 μM) and IL-1β (IC_{50}: 12.15 ± 1.36 μM).

1. Introduction

Triterpenes represent diverse class of natural products, which on account of their omnipresence constitute as major components of a number of medicinal plants. These metabolites show a wide range of biological activities and are promising lead candidates for the development of new drugs [1]. Among the triterpenes, the most interesting and structurally diverse skeletons are the myrrh group of triterpenes, which are bicyclic polypodanes and are highly specific to the *Commiphora* genus of Burseraceae family. The gum resin of *Commiphora mukul* has been used in Indian Ayurvedic system for the treatment of rheumatoid arthritis, inflammation, obesity and lipid disorders and also exhibits a broad range of pharmacological effects including cytotoxic, anaesthetic, anti-inflammatory, antimicrobial and antidiabetic [2]. The major bioactive molecules of *Commiphora mukul* are myrrh triterpenes such as myrrhanone A, B & C and myrrhanol A, B & C, which were reported to exhibit significant anti-inflammatory and anticancer activities [3–6]. Interestingly, myrrhanone A and myrrhanol A were reported to alleviate inflammation in adjuvant-induced air-pouch granuloma of mice [7]. Generally, the isolated natural products are found with both moderate or weak biological activities and need to be modify chemically to enhance their therapeutic potential [8]. The semi synthetically derived molecules from parent natural products continues to play an important role in the drug discovery process and exhibit a high impact on their biological activity [9]. Recently, we have reported the anticancer activity of myrrhanone C analogues with significantly enhanced activities than the parent myrrhanone C [10,11]. Although, two of its structurally related metabolites such as myrrhanones A & B isolated from *Commiphora mukul*, they are totally unexplored in both chemical and biological point of views. Hence, these molecules have

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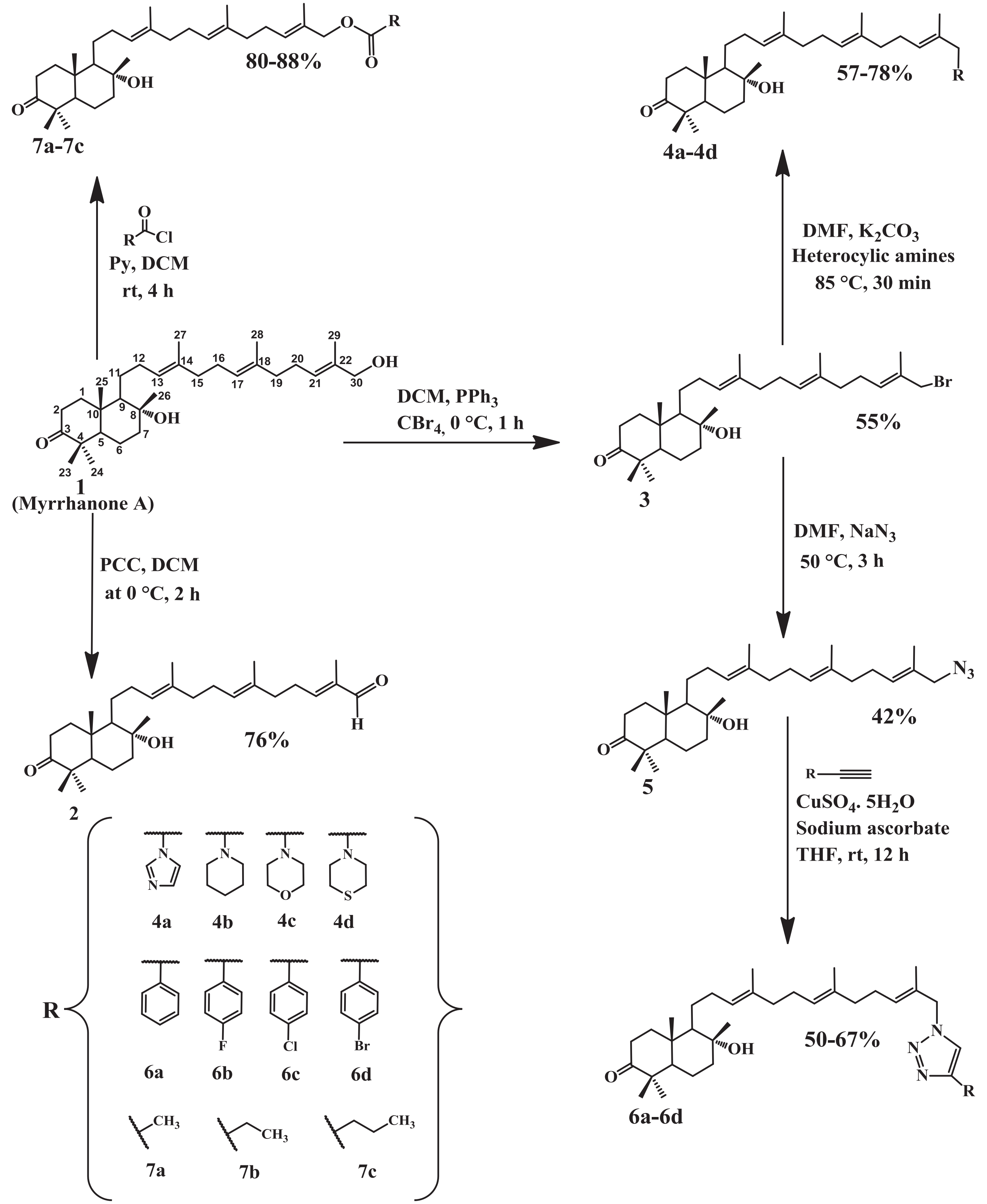
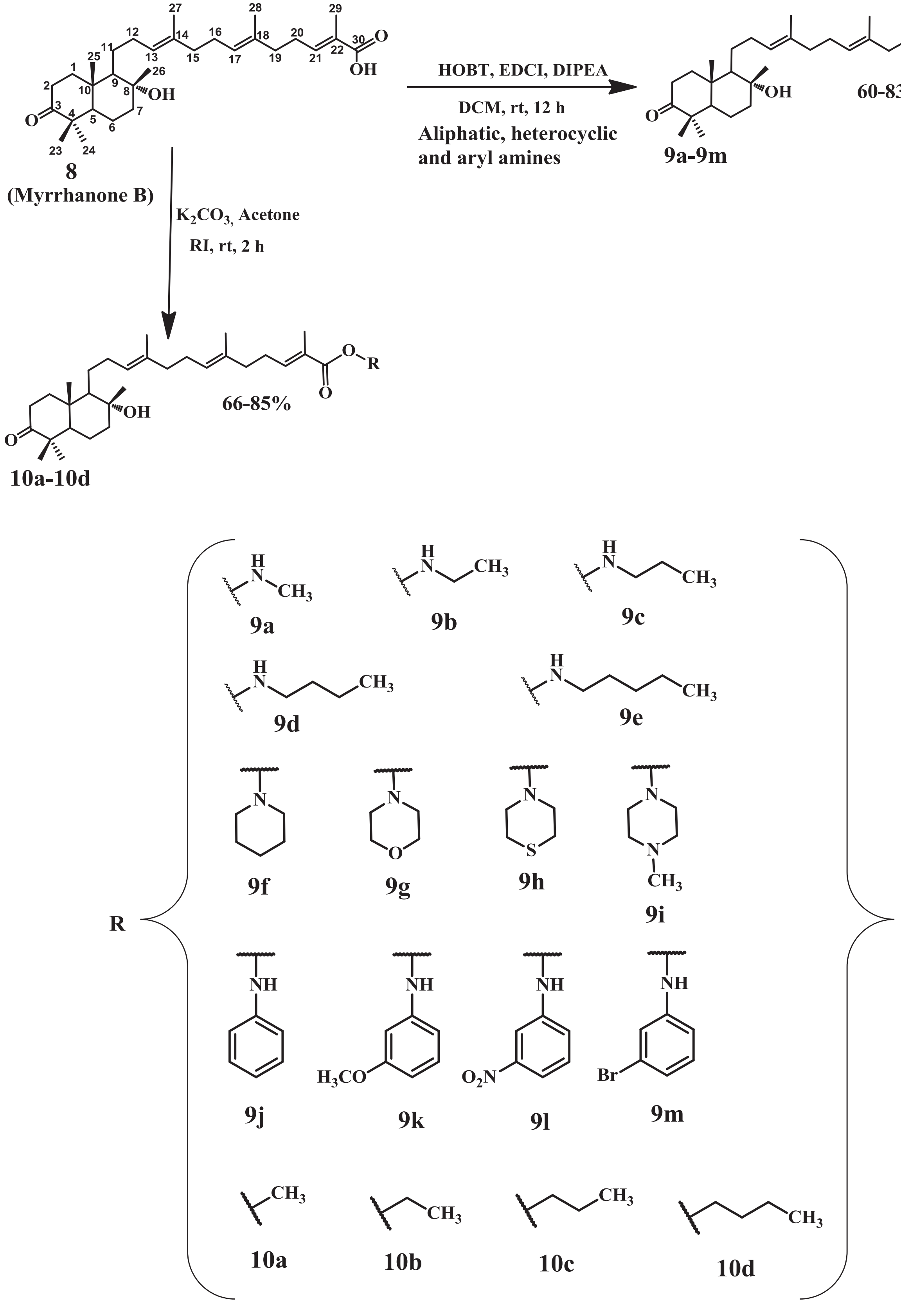


Scheme 1.

tremendous scope in synthesising library of novel analogues for drug discovery. With this background in view, myrrhanones A & B were now taken up as scaffolds for chemical modification and detailed bio evaluation studies. These molecules have very interesting structural features with a common bicyclic core, C-3 keto functionality in ring A and a triene side chain. But they differ significantly in their side chain



Scheme 2.

terminal functionality. In case of myrrhanone A, it has hydroxyl functionality, whereas myrrhanone B has a carboxylic acid group. In this study, we focused our attention towards the synthesis of some diverse analogues using terminal hydroxyl and carboxyl groups of myrrhanones A & B to investigate and understand the key functionalities required for enhanced anticancer and anti-inflammatory activities.

2. Results and discussion

2.1. Chemistry

The protocols employed for the synthesis of diverse analogues of myrrhanones A and B are presented in Schemes 1 and 2. Initially, the primary hydroxyl group present in compound **1** was transformed to aldehyde, bromo and ester analogues by employing efficient and high yielding methodologies (Scheme 1). Compound **1**, when treated with pyridinium chlorochromate (PCC) in dichloromethane at 0 °C for 2 hr. afforded the corresponding aldehyde (**2**) in 76% yield (IR: 1702 cm^{-1}; ^{1}H: δ 9.34; ^{13}C: δ 195.34) [12]. Similarly, compound **1** when treated with CBr_4 in presence of triphenyl phosphine in dichloromethane afforded the bromo compound **3** in 55% yield [13]. Further, compound **1** when treated with acyl chlorides (acetyl, propionyl, butyryl) in presence of pyridine in dichloromethane yielded the corresponding esters (**7a-7c**) in 80–88% yield (IR: 1734–1737 cm^{-1}; ^{13}C: δ 171.05–174.50) [18]. The key bromo compound **3** on coupling with various heterocyclic amines (imidazole, piperidine, morpholine and thiomorpholine) in presence of potassium carbonate in N,N-dimethylformamide (DMF) afforded the title compounds (**4a-d**) in 57–78% yield [14,15]. These compounds showed the characteristic NMR signals of $-CH_2N-$ group [**4a** ^{1}H: δ 4.38, ^{13}C: δ 55.11; **4b-4d** ^{1}H: δ 2.82–2.83, ^{13}C: δ 67.73–67.90]. Similarly, compound **3** when treated with sodium azide in dry DMF at 50 °C afforded the key azido compound **5** [16] in 42% yield. Subsequent treatment of compound **5** with substituted phenyl acetylenes in dry THF in presence of copper sulphate and sodium ascorbate at room temperature afforded the corresponding 1,2,3-triazoles (**6a-6d**) in 50–67% yield [17]. These compounds showed the characteristic 1,2,3-triazole ring NMR signals [^{1}H: δ 4.86–5.07, 7.65–7.71; ^{13}C: δ 118.32–119.40, 146.86–147.50]. In Scheme 2, a series of homologous amides (**9a-9m**) were synthesized by coupling of compound **8** with aliphatic, aromatic and heterocyclic amines (morpholine, thiomorpholine, piperidine and *N*-methyl piperazine) in presence of EDCI- HOBt - DIPEA coupling medium in moderate to good yields (60–83%) [19].All the synthesized amides showed the characteristic amide carbon signals between δ 167 and 168 Finally, a series of aliphatic esters (linear chains) were prepared by treating compound **8** in acetone with alkyl iodides in the presence of anhydrous potassium carbonate to afforded compounds (**10a-10d**) in moderate to good yields (66–85%) [20]. The synthesized esters showed characteristic spectral values in IR: 1705–1709 cm^{-1} and ^{13}C: δ 168.14–168.52.

2.2. Biology

2.2.1. In vitro cytotoxicity activity

The newly synthesized 29 analogues (**2-10d**) were evaluated for their anticancer activity against a panel human cancer cell lines, namely, DU145 (Prostate), HT-29 (Colo-rectal), MCF-7 (Breast), Hela (Cervical) and U87MG (Glioblastoma) along with normal lung cell line (L132) by using MTT assay [21]. The results are summarized in Table 1 and presented as the concentration of drug inhibiting 50% cell growth (IC_{50}). Preliminary results indicated that most of the analogues exhibited moderate to good activity against tested cancer cell lines. The results also demonstrated that the existence of a structural constraint such as morpholine, thiomorpholine, *n*-methyl piperazine, piperidine and imidazole at C-30 is favorable to the inhibitory activity, which is exemplified by compounds **4a, 4b, 9f, 9g** and **9i**. Similarly, compound **9d** in the amide series exhibited potent inhibitory activity. However, most interestingly, compounds **4b, 9d** and **9i** were the most promising derivatives with IC_{50} values **4.65 ± 1.28, 5.48 ± 0.13** and **6.63 ± 1.39** μM (Fig. 1). The piperidine compound **4b** showed highest activity against MCF-7, which is about 4–5 folds more potent than its parent myrrhanone A [**1,** IC_{50} (μM) 23.40 ± 1.16]. Furthermore, compound **9d** was found to be 15–18 folds more potent against HT-29 than the parent myrrhanone B [**8,** IC_{50} (μM) 93.58 ± 3.29]. In addition, N- methyl piperazine analogue **9i** exhibited about 12–13 folds higher activity against DU145 than myrrhanone B [**8,** IC_{50} (μM) 83.55 ± 3.28]. Hence, compounds **4b, 9d** and **9i** can be considered as lead molecules with potent anticancer activity and these molecules taken up for further apoptosis studies.

2.2.1.1. Cell cycle analysis. The growth inhibitory effect of active compounds was studied by arresting the cell or induction of apoptosis at specific phase in cell cycle analysis [22]. The compounds **4b**, **9d** and **9i** were treated against MCF-7, HT-29 and DU145 at 2.5 μM, 5 μM and 10 μM respectively for 24 h by using propidium iodide staining method and those samples were further analyzed by flow cytometry. The biological results revealed that the compounds **4b**, **9d** and **9i** exhibited good anticancer activity and cells (MCF-7, HT-29 and DU145) were significantly arrested in the G0/G1 in a concentration dependent manner (Fig. 2).

2.2.1.2. Phase contrast microscopy. This technique has been used to study in detail about cell viability and apoptosis induction [23]. The compounds **4b**, **9d** and **9i** were treated against MCF-7, HT-29 and DU145 cells in 2.5 μM, 5 μM and 10 μM concentrations respectively. These cells were observed and images were captured using phase contrast microscope. The results reveled that the increasing concentration of compounds led to the decreased number of viable cells compared to control, and this was confirmed by observing morphological changes such as membrane blebbing, nuclear shrinkage and apoptotic body formation (Fig. 3).

2.2.1.3. ***Acridine orange/ethidium bromide** (AO/EB) **staining***. The morphological changes induced by the compounds **4b**, **9d** and **9i** in MCF-7, HT-29 and DU145 cells respectively were studied through fluorescence microscopy using AO/ EB staining technique. Acridine orange/ethidium bromide (AO/EB), a fluorescent staining assay, was performed to identify the nuclear changes and to distinguish live, apoptotic and necrotic cells [24]. The cells were viewed under florescence microscopic and were counted to quantify apoptosis. AO is a vital dye and it will stain both living and dead cells emitting green florescence, while EB will stain only cells that have lost their membrane integrity and emitting tinge orange florescence. It can be interpreted from (Fig. 4) that the control cells showed the normal healthy morphology with intact nuclear architecture and appeared green in color. The fluorescence microscopic images of compounds **4b**, **9d** and **9i** gave clear information about morphological changes which are the characteristic features of apoptotic cells such as cell shrinkage, membrane blebbing and chromatin condensation with destructive fragmentation of the nucleus and apoptotic body formation. The results confirm that the compounds **4b**, **9d** and **9i** induced cell death in MCF-7, HT-29 and DU145 cancer cells by apoptosis.

2.2.1.4. DAPI staining. 4′,6-diamidino-2-phenylindole (DAPI) is a popular fluorescent dye that binds strongly to nucleus and detect the nuclear damage or chromatin condensation [25]. In DAPI nuclear staining, the apoptotic cells emit as bright colored fluorescence owing to the condensed nucleus which is a distinctive apoptotic characteristic. Our interest is to examine clearly the morphological changes of such as nuclear damage or chromatin condensation induced by the compounds **4b**, **9d** and **9i** in MCF-7, HT-29 and DU145 cells, which were appeared as a bright blue florescent (Fig. 5). The DAPI nuclear staining technique was performed according to the earlier reported method.

2.2.1.5. Mitochondrial membrane potential ($\Delta\Psi m$). Mitochondrial membrane potential is a key function for indicating of cell health and injury. In general, florescent dyes are frequently used to measure mitochondrial membrane potential for monitoring important physiologic mitochondrial parameter changes in cells [26]. The effect of compounds **4b**, **9d** and **9i** on mitochondrial membrane potential was

Table 1
Anticancer results (IC_{50}: µM) of synthesized compounds (**2-10d**).

Compounds	IC_{50} (µM)					
	DU145	HT-29	MCF-7	Hela	U87MG	L132
1	11.66 ± 1.33	13.56 ± 3.28	23.40 ± 1.16	> 150	33.89 ± 5.09	116.18 ± 3.46
2	20.63 ± 1.37	14.98 ± 1.49	31.56 ± 1.28	128.13 ± 2.14	42.21 ± 4.70	54.70 ± 2.75
4a	**7.74 ± 0.37**	10.01 ± 2.50	13.11 ± 2.05	31.93 ± 2.84	24.88 ± 1.54	22.05 ± 0.09
4b	8.42 ± 0.12	15.37 ± 1.35	**4.65 ± 1.28**	26.81 ± 1.02	10.25 ± 2.01	114.76 ± 5.61
4c	33.17 ± 1.08	11.14 ± 3.25	40.71 ± 1.82	72.81 ± 4.81	86.81 ± 4.39	4.33 ± 0.39
4d	27.18 ± 1.93	17.17 ± 1.91	86.70 ± 0.46	> 150	117.66 ± 1.67	149.01 ± 4.19
6a	27.31 ± 3.15	44.85 ± 2.24	135.82 ± 2.15	58.26 ± 1.58	> 150	> 150
6b	34.18 ± 2.09	48.00 ± 1.91	36.21 ± 1.61	136.47 ± 4.28	> 150	87.11 ± 1.78
6c	> 150	57.71 ± 0.73	> 150	> 150	> 150	> 150
6d	120.66 ± 4.33	76.58 ± 3.25	> 150	111.93 ± 3.11	> 150	> 150
7a	10.26 ± 1.13	42.24 ± 4.12	30.63 ± 1.36	> 150	39.64 ± 2.96	> 150
7b	29.04 ± 2.02	15.81 ± 2.18	46.34 ± 1.84	93.71 ± 3.71	97.08 ± 0.39	148.89 ± 1.82
7c	32.00 ± 3.19	44.21 ± 3.08	75.23 ± 2.35	> 150	> 150	> 150
8	83.55 ± 3.28	93.58 ± 3.29	97.36 ± 2.69	> 150	> 150	> 150
9a	19.43 ± 1.22	21.43 ± 1.31	28.73 ± 1.06	> 150	110.35 ± 3.11	63.55 ± 3.44
9b	16.34 ± 0.92	14.50 ± 2.63	15.79 ± 1.34	110.22 ± 1.39	> 150	> 150
9c	19.98 ± 3.49	15.12 ± 1.35	16.84 ± 1.99	91.95 ± 1.46	> 150	> 150
9d	17.34 ± 0.71	**5.48 ± 0.13**	11.13 ± 1.36	86.00 ± 1.31	> 150	> 150
9e	> 150	12.66 ± 1.20	78.72 ± 2.60	114.27 ± 3.06	> 150	112.06 ± 1.60
9f	8.33 ± 2.18	13.47 ± 2.32	14.03 ± 0.64	44.75 ± 4.06	30.64 ± 2.19	50.76 ± 4.86
9g	8.79 ± 2.39	15.36 ± 0.77	16.53 ± 2.03	15.62 ± 2.10	21.21 ± 0.91	23.06 ± 3.16
9h	11.82 ± 2.41	94.63 ± 2.35	33.23 ± 2.54	> 150	37.16 ± 3.71	92.54 ± 5.13
9i	**6.63 ± 1.39**	12.00 ± 0.62	12.02 ± 1.94	13.93 ± 1.48	21.87 ± 4.30	19.46 ± 1.69
9j	46.32 ± 3.16	14.02 ± 0.72	96.72 ± 1.29	121.27 ± 2.97	> 150	> 150
9k	> 150	55.79 ± 3.21	108.37 ± 1.37	107.13 ± 1.37	> 150	> 150
9l	94.37 ± 1.19	53.25 ± 2.68	> 150	143.99 ± 4.31	> 150	> 150
9m	> 150	> 150	> 150	> 150	> 150	> 150
10a	29.95 ± 0.96	14.59 ± 0.89	40.52 ± 1.84	103.06 ± 1.88	> 150	148.80 ± 1.43
10b	34.88 ± 3.24	59.92 ± 3.21	> 150	57.97 ± 2.17	> 150	141.75 ± 1.53
10c	45.21 ± 4.23	> 150	106.82 ± 2.01	> 150	> 150	> 150
10d	> 150	47.34 ± 4.62	114.26 ± 1.64	14.83 ± 1.57	> 150	141.12 ± 3.21
Docetaxel	0.26 ± 0.01	0.66 ± 00003	0.82 ± 0.006	0.04 ± 0.009	0.18 ± 0.001	0.01 ± 0.018

Bold values indicate the potent ones.

assessed by staining with lipophilic cationic florescent JC-1 dye. In the healthy cells, the polarized mitochondria stains emit red florescence (590 nm) due to formation of J-aggregates from JC-1 monomers, while depolarized mitochondria stains emit green light (540 nm) because of collapses mitochondrial membrane potential (Fig. 6). The results indicated loss of mitochondrial membrane potential increasing with increasing concentrations of compounds **4b**, **9d** and **9i** than compared with control.

2.2.1.6. Reactive oxygen species (ROS). The generation of reactive oxygen species play important role in the immune system, which is well and typical characteristic mechanisms of many chemotherapeutic agents by initiating oxidative damage to the mitochondrial membrane potential and permeability [27]. The ROS generation causes oxidative stress that results injury to all the important cellular components like proteins, DNA membrane which can implicate for apoptotic induction. Therefore, DCFDA staining method has been used for generation of intracellular reactive oxygen species (ROS) of compounds **4b**, **9d** and **9i** on MCF-7, HT-29 and DU145 cells respectively. Intracellular ROS measurements by using DCFDA probe showed that ROS levels were increased significantly with increasing concentration of compounds 4b, 9d and 9i. These compounds were treated for 6 h, which revealed increasing DCFDA fluorescence in a dose dependent manner, indicating the capability of compounds in accumulating ROS levels (Fig. 7). On the other hand, compounds were treated with *N*-acetyl cysteine (NAC) decreased fluorescence intensity, which indicating the compounds induced cytotoxicity by ROS generation. Moreover, H_2O_2 treatment of MCF-7, HT-29 and DU145 cells led to the increased fluorescence when compared to the control due to the generation of radicals.

2.2.2. Anti-inflammatory activity

The newly synthesized 29 analogues were evaluated for their *in vitro* anti-inflammatory activity against TNF-α and IL-1β by using LPS induced inflammation model in U937 cell lines. The results were compared with those of parent molecules and are shown in Tables 2 and 3. Biological results interesting to observe that some of title compounds **2**, **4a, 9a-9c** and **9f-9i** displayed remarkable anti-inflammatory activity (Fig. 1). Compounds **2**, **4a, 9a-9c** and **9f-9i** showed good activity against TNF-α with IC_{50} values ranging between 9.39 and 20.23 µM and moderately active against IL-1β with IC_{50} values between 12 and 50 µM. Most interestingly, compound **9c** has aliphatic amide bond with three carbon chain displayed strong inhibitory activity against TNF-α (IC_{50} = 10.02 ± 2.13 µM) compared to myrrhanone B (**8,** IC_{50} = 36.87 ± 2.06 µM). Similarly, compound **9g** has morpholine contain amide bond showed higher inhibitory activity against TNF-α (IC_{50} = 10.53 ± 0.48 µM) then compared to myrrhanone B (**8,** IC_{50} = 36.87 ± 2.06 µM). Surprisingly, on the basis of results it was observed that compound **2** with an aldehyde group at terminal bond of side chain possess to display enhanced anti-inflammatory activity against both TNF-α (IC_{50} = 9.39 ± 0.44 µM) and IL-1β (IC_{50} = 12.15 ± 1.36 µM) than the parent compounds, myrrhanone A [**1,** IC_{50} (µM) TNF-α = 21.25 ± 1.47; IL-1β = 24.36 ± 1.12] and myrrhanone B [**8,** IC_{50} (µM) TNF-α = 36.87 ± 2.06; IL-1β = 24.63 ± 1.56].

3. Conclusion

In summary, twenty nine novel analogues of myrrhanones A & B were synthesized by chemical modification of their hydroxyl and carboxylic acid functionalities. All the synthesized compounds were evaluated for their cytotoxic potential against a panel human cancer cell

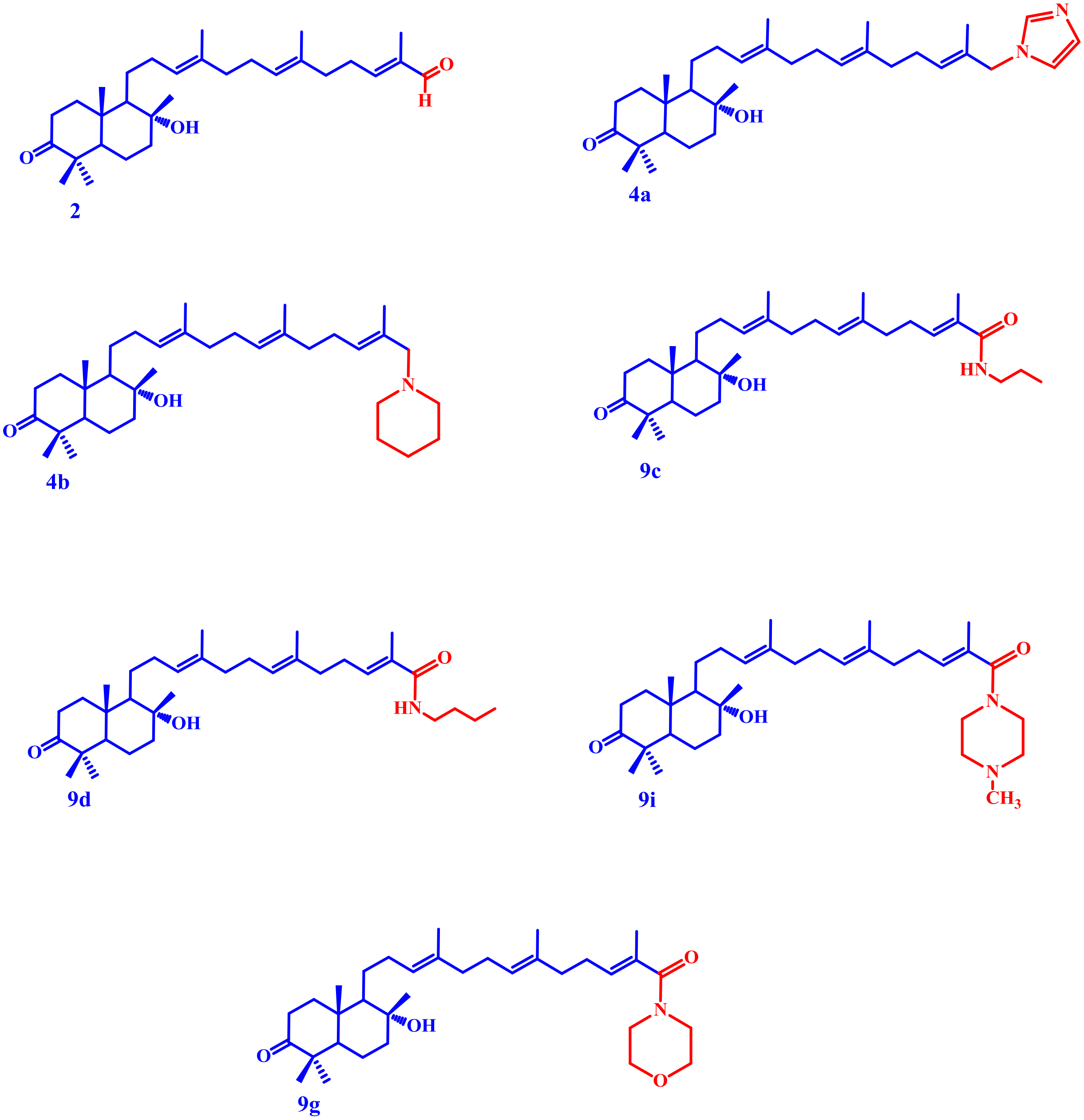
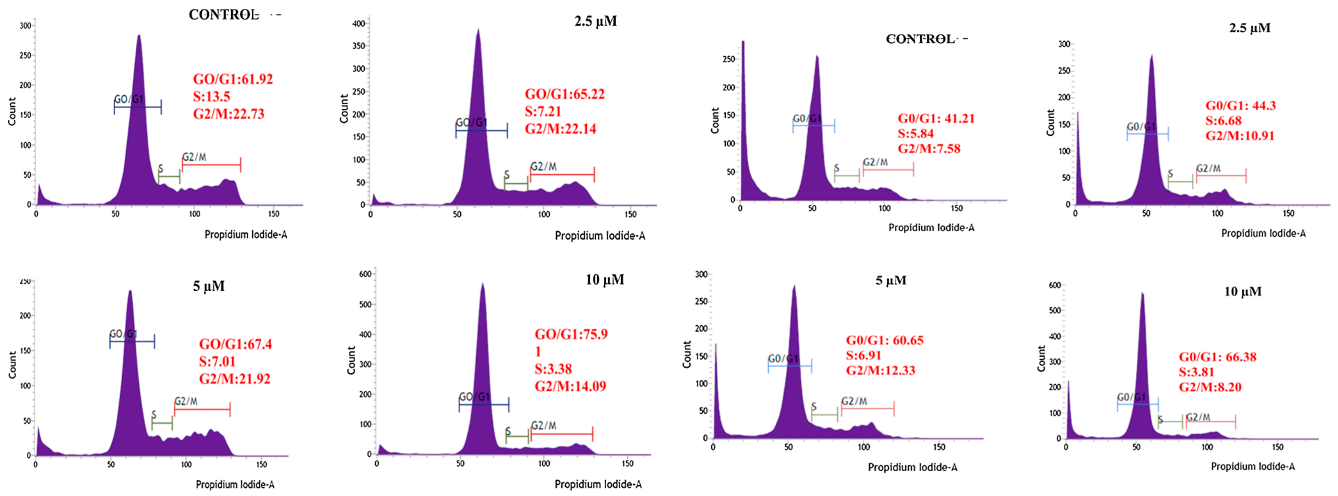


Fig. 1. Potent anticancer and anti-inflammatory analogues of myrrhanones A & B.

lines (DU145, HT-29, MCF-7, Hela and U87MG) along with lung normal cell line. Interestingly, the screening results revealed that compounds **4b, 9d** and **9i** showed potent cytotoxicity against MCF-7, HT-29 and DU145 cell lines with IC_{50} values less than 7 µM and found superior than the parent compounds **1** and **8**. Further, compounds **4b, 9d** and **9i** induce apoptosis in MCF-7, HT-29 and DU145 cells respectively and arrested in G0/G1 phase. Hence, these three compounds can be considered as good candidates for further development.. All the synthesized compounds were also screened for their anti-inflammatory activity against TNF-α and IL-1β. and found compounds **2**, **9c** and **9g** potent with significant inhibitory activity against TNF-α. Based on the screening data, it can be concluded that the presence of an aldehyde group at C-30 position (**2**) exhibited prominent anti-inflammatory activity against both TNF-α and IL-1β than the parent myrrhanone A (**1**) and myrrhanone B (**8**).

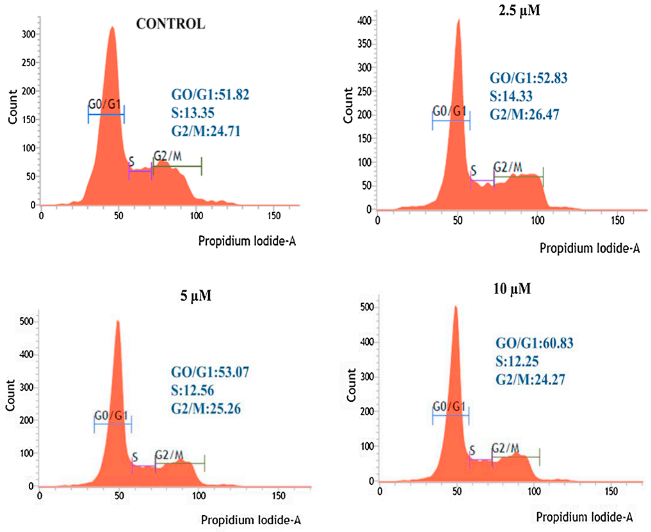
4. Experimental protocols

All solvents were distilled prior to use. All reagents and chemicals were purchased from Sigma-Aldrich and used without further purification. The progress of all reactions was monitored by thin layer chromatography (TLC) using silica gel 60 F254 plates (Merck). Visualization was accomplished with UV light (254 mm) and spraying with sulfuric acid/ methanol followed by heating. Purification of the compounds was carried out by column chromatography using silica gel 60–120 mess (Merck). IR spectra were recorded in KBr disks on a Nicolet 740 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker AVANCE-I 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) or Bruker AVANCE-III 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) NMR instruments using TMS as an internal standard and $CDCl_3$ as solvent. Chemical shifts are expressed in parts per million (δ) values and coupling constants (*J*)



(4b, MCF-7)

(9d, HT-29)



(9i, DU145)

Fig. 2. Effect of compounds **4b, 9d** and **9i** on MCF-7, HT-29 and DU145 cells respectively in cell cycle analysis by using propidium iodide staining method after 24 h of treatment at 2.5 µM, 5 µM and 10 µM concentrations. Cell population in each cell cycle phase was numerically depicted.

are given in Hertz (Hz). Mass spectra were carried on an Agilent ESI-QTAF spectrometer and HRMS experiments were performed using an ORBITRAP by Thermo scientific instrument. The following abbreviations were used to explain for NMR signals. s = singlet, d = doublet, t = triplet, m = multiplet, J = coupling constant.

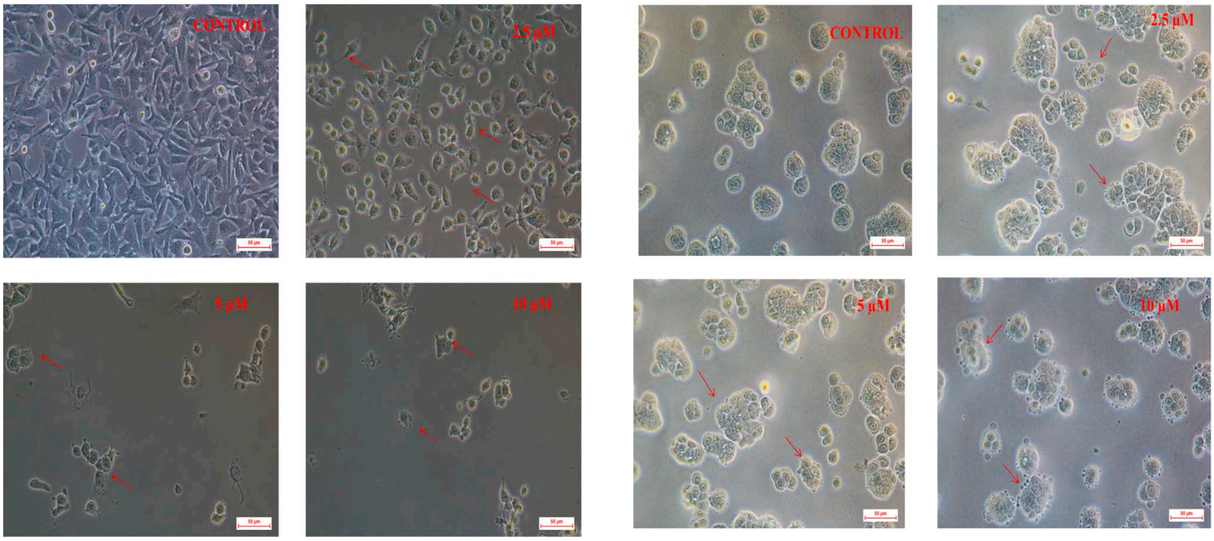
4.1. *Chemistry*

4.1.1. *Isolation of myrrhanone A (1) and myrrhanone B (8)*

The *Commiphora mukul* gum resin was collected through Baidyanath Ayurvedic Pharmacy, Patna, India. The resin was dried and powdered in a mixer. The powdered material (1.0 kg) was exhaustively extracted with *n*-hexane (5.0 l) by using soxhlet apparatus for 24 h. The *n*-hexane soluble components were concentrated under reduced pressure to give yellowish brown gummy extract (180 g). The resulting gummy extract (100 g) was fractionated by column chromatography using silica gel (100–200 mesh) with *n*-hexane:ethyl acetate as the mobile phase under gradient conditions. In the solvent polarity *n*-hexane-ethyl acetate (80:20), compound **1** was eluted as pale yellow oil, whereas in the same solvent system with polarity of 75:25, compound **8** was eluted as pale yellow oil. The structures of the isolated compounds **1** and **8** were confirmed by their spectral data (^{1}H NMR, ^{13}C NMR, HRMS and IR) and by comparing with the reported values [5,7].

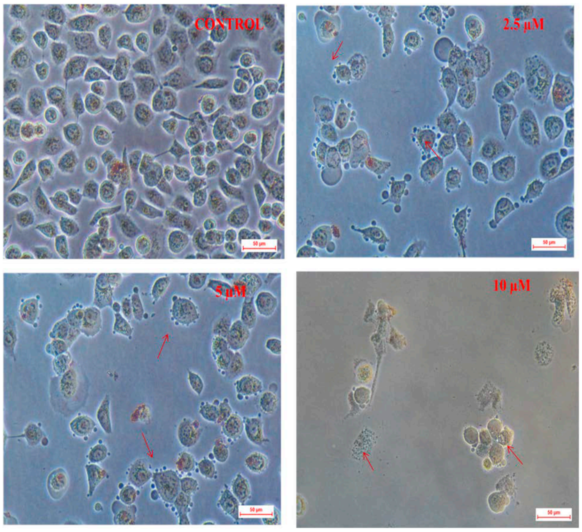
4.1.1.1. *(5S,8R,9R,10S)-3-oxo-8,30-dihydroxypolypoda-13E,17E,21E-triene (**1**)*. Yield 0. 0.53%; pale yellow oil; Rf: 0.5 (30% *n*-hexane:ethyl acetate); $[\alpha]_D^{28}$ + 12.00 (MeOH); IR (KBr, cm^{-1}): 3405, 2927, 1701, 1455, 1385, 1218, 1079, 1007, 925, 759; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3-25), 1.02 (s, 3H, CH_3-24), 1.10 (s, 3H, CH_3-23), 1.20 (s, 3H, CH_3-26), 1.34–1.57 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.60 (s, 6H, CH_3-28, CH_3-27), 1.66 (s, 3H, CH_3-29), 1.90–2.15 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.40 (m, 1H, CH-2), 2.60 (m, 1H, CH-2), 4.00 (s, 2H, CH_2-30), 5.11 (t, 1H, J = 6.86 Hz, CH-13), 5.16 (t, 1H, J = 6.71 Hz, CH-17), 5.39 (t, 1H, J = 6.86 Hz, CH-21). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.90 (C_3), 135.30 (C_{14}), 134.62 (C_{18}), 134.54 (C_{22}), 125.80 (C_{21}), 124.69 (C_{13}), 124.40 (C_{17}), 73.62 (C_8), 68.78 (C_{30}), 60.22 (C_9), 55.04 (C_5), 47.44 (C_4), 43.68 (C_7), 39.54 (C_{19}), 39.22 (C_{10}), 38.50 (C_1), 38.23 (C_{15}), 33.90 (C_2), 31.08 (C_{12}), 26.40 (C_{20}), 26.18 (C_6), 26.04 (C_{16}), 25.67 (C_{11}), 23.50 (C_{26}), 21.28 ($C_{23,}$ C_{24}), 16.15 (C_{27}), 15.94 (C_{28}), 14.77 (C_{25}), 13.65 (C_{29}).

ESI-HRMS Calcd for $C_{30}H_{50}O_3$ [M + Na] + 481.3652, found 481. 3647.



(**4b**, **MCF-7**)

(**9d**, **HT-29**)



(**9i**, **DU145**)

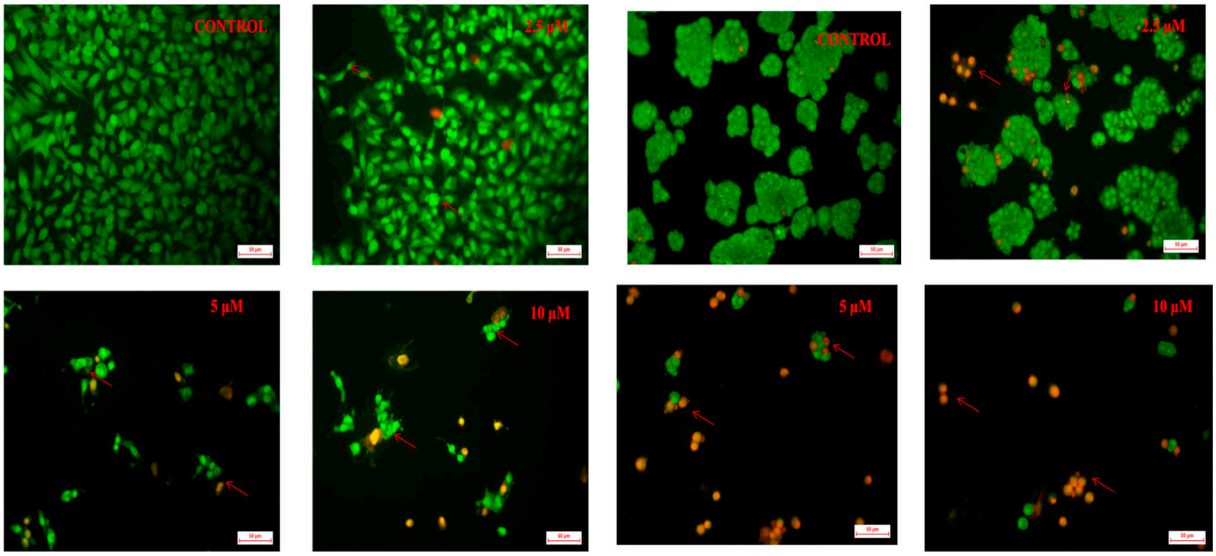
Fig. 3. Phase contrast imaging: Effect of compounds **4b, 9d** and **9i** on the viability of MCF-7, HT-29 and DU145 cells after 24 h treatment at various (2.5 µM, 5 µM and 10 µM) concentrations.

*4.1.1.2. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-carboxypolypoda-13E,17E,21E-triene (**8**).* Yield 0.58%; pale yellow oil; $R_f = 0.46$ (30% *n*-hexane:ethyl acetate); $[\alpha]_D^{26} + 11.96$ (MeOH); IR (KBr, cm^{-1}): 3419, 2931, 2861, 1696, 1648, 1452, 1385, 1277, 1184, 1126, 1080, 923, 760, 553; ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3-25), 1.02 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.22 (s, 3H, CH_3-26), 1.44–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.57 (s, 3H, CH_3-28), 1.60 (s, 3H, CH_3-27), 1.82 (s, 3H, CH_3-29), 1.90–2.13 (m, 12H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.30 (m, 2H, CH_2-20), 2.40 (m, 1H, CH-2), 2.60 (m, 1H, CH-2), 5.10 (m, 2H, CH-13, CH-17), 6.81 (t, 1H, $J = 7.32$ Hz, CH-21). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.98 (C_3), 172.25 (C_{30}), 144.21 (C_{21}), 134.69 (C_{18}), 133.44 (C_{14}), 127.03 (C_{22}), 125.25 (C_{13}), 124.91 (C_{17}), 74.22 (C_8), 60.31 (C_9), 55.03 (C_5), 47.46 (C_4), 43.48 (C_7), 39.34 (C_{19}), 38.52 (C_{10}), 38.18 (C_1), 37.94 (C_{15}), 33.91 (C_2), 31.27 (C_{12}), 26.98 (C_{20}), 26.17 (C_6), 26.06 (C_{16}), 25.73 (C_{11}), 23.44 (C_{26}), 21.30 ($C_{23,}$ C_{24}), 16.05 (C_{27}), 15.83 (C_{28}), 14.77 (C_{25}), 12.09 (C_{29}); ESI-HRMS Calcd for $C_{30}H_{48}O_4$ $[M + Na]^+$ 495.3447, found 495.3444.

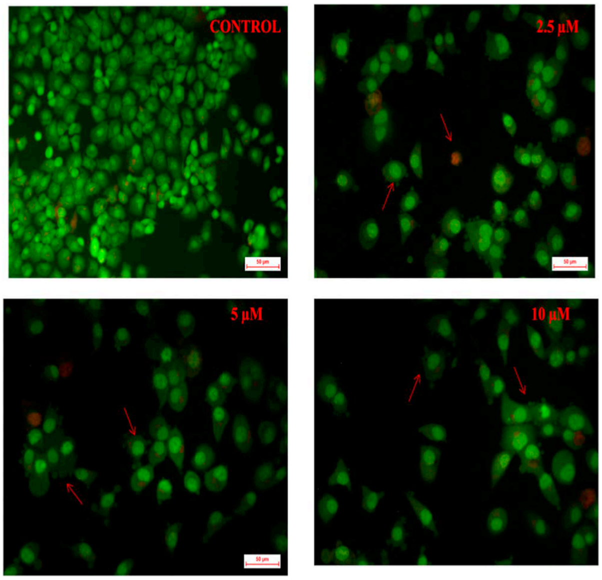
*4.1.2. Preparation of compound (**2**)*

To a solution of compound **1** (50 mg, 0.11 mmol) in dry DCM (2 mL), PCC (87 mg, 0.40 mmol) was added and stirred at 0 °C for 2 h. After completion of the reaction, it was extracted with DCM (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography with *n*-hexane:ethyl acetate (90:10 v/v) to obtain the pure compound **2.**

4.1.2.1. (5S,8R,9R,10S)-3-oxo-8-hydroxypolypoda-13E,17E,21E-trienal). Yield 76%; light yellow semi solid; $R_f = 0.52$ (30% *n*-hexane:ethyl acetate); IR (KBr cm^{-1}): 3447, 2926, 2856, 1702, 1457, 1383, 1079, 765; ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H, CH_3-25), 0.99 (s, 3H, CH_3-24), 1.07 (s, 3H, CH_3-23), 1.17 (s, 3H, CH_3-26), 1.42–1.51 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.57 (s, 3H, CH_3-28), 1.60 (s, 3H, CH_3-27), 1.71 (s, 3H, CH_3-29), 1.88–2.16 (m, 12H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.34–2.63 (m, 4H, CH_2-2, CH_2-20), 5.12 (m, 2H, CH-13, CH-17), 6.44 (t, 1H, $J = 6.98$ Hz, CH-21),



(4b, MCF-7) **(9d, HT-29)**



(9i, DU145)

Fig. 4. Cellular morphological changes (such as apoptotic bodies, membrane blebbing and dead cells) of compounds **4b, 9d** and **9i** in MCF-7, HT-29 and DU145 cells were investigated by AO/EB staining using fluorescence microscopy at different concentrations (2.5 µM, 5 µM and 10 µM).

9.34 (Brs, 1H, aldehyde-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.85 (C_3), 195.34 (C_{30}), 154.63 (C_{21}), 139.25 (C_{22}), 135.18 (C_{18}), 133.32 (C_{14}), 125.50 (C_{13}), 124.80 (C_{17}), 73.60 (C_8), 60.34 (C_9), 55.10 (C_5), 47.47 (C_4), 43.75 (C_7), 39.50 (C_{19}), 38.54 (C_{10}), 38.26 (C_1), 37.91 (C_{15}), 33.92 (C_2), 31.15 (C_{12}), 27.30 (C_{20}), 26.47 (C_6), 26.23 (C_{16}), 25.70 (C_{11}), 23.57 (C_{26}), 21.31 ($C_{23,}$ C_{24}), 16.15 (C_{27}), 15.87 (C_{28}), 14.79 (C_{25}), 9.20 (C_{29}); ESI-HRMS Calcd for $C_{30}H_{48}O_3$ $[M+Na]^+$ 479.3505, found 479.3495.

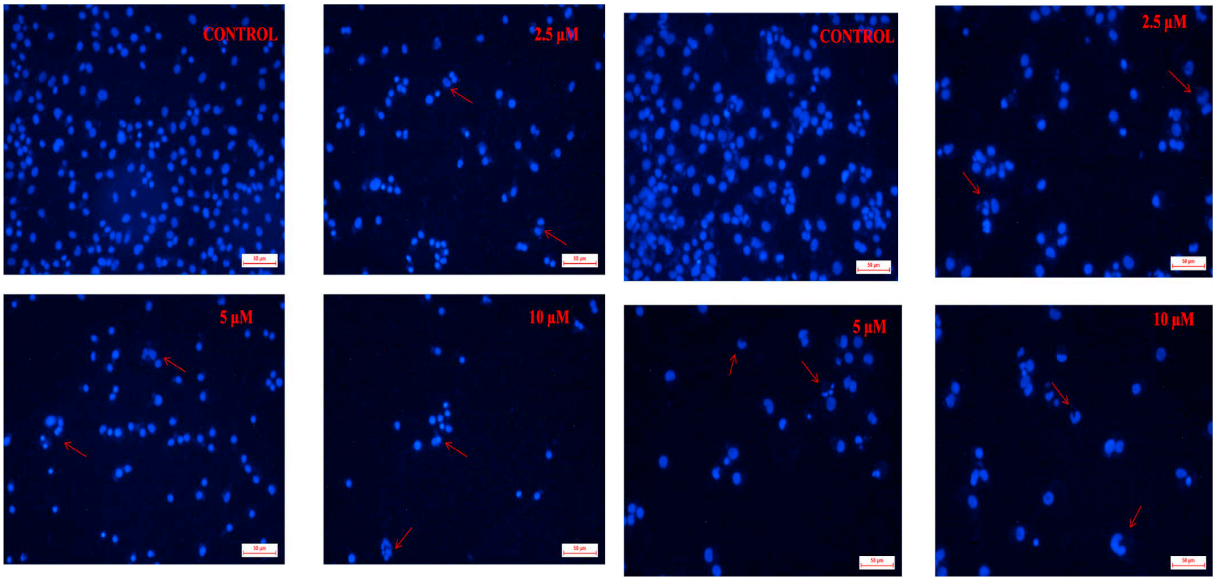
4.1.3. *Preparation of key intermediate (**3**)*

To a solution of compound **1** (250 mg, 0.54 mmol) in dry DCM (2 mL), PPh_3 (110 mg, 0.42 mmol) and CBr_4 (98 mg, 0.30 mmol) were added at 0 °C and the reaction mixture was stirred for 1 h. After completion of the reaction, it was extracted with DCM (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography with *n*-hexane:ethyl acetate (95:5 v/v) to furnish the pure compound in 55% yield.

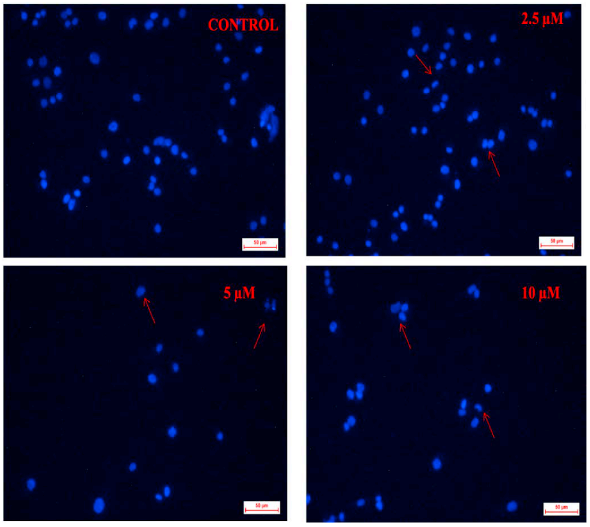
4.1.4. *General procedure for the synthesis of compounds (**4a-4d**)*

To a stirred solution of compound **3** (50 mg, 0.09 mmol) in dry DMF (2 mL)**,** K_2CO_3 (28 mg, 0.20 mmol) and appropriate amine (1.68 mmol) were added and the resulting mixture was stirred at 85 °C for 30 min. After completion of the reaction, it was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography with *n*-hexane:ethyl acetate (60:40 to 50:50 v/v) to furnish the pure compounds in 57–78% yield.

4.1.4.1. (5S,8R,9R,10S)-8-hydroxy-30-(1H-imidazol-1-yl) polypoda-13E,17E,21E-triene-3- one (4a). Yield 71%; light yellow semi solid; $R_f = 0.50$ (40% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3427, 2924, 2856, 1700, 1650, 1503, 1453, 1385, 1224, 1078, 768, 663, 582; ^{1}H



(4b, MCF-7) **(9d, HT-29)**

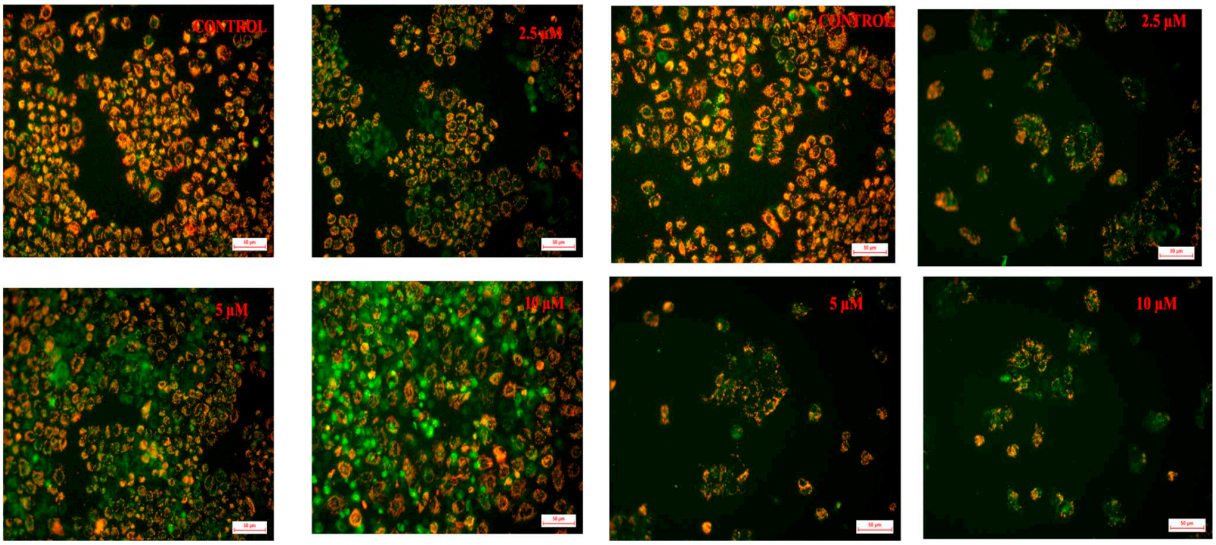


(9i, DU145)

Fig. 5. Nuclear morphological changes were determined by DAPI staining in MCF-7, HT-29 and DU145cells by treated with varied concentrations (2.5 µM, 5 µM and 10 µM) of compounds **4b**, **9d** and **9i**. The cells were clearly observed apoptotic characteristics such nuclear fragmentation and condensed nuclei.

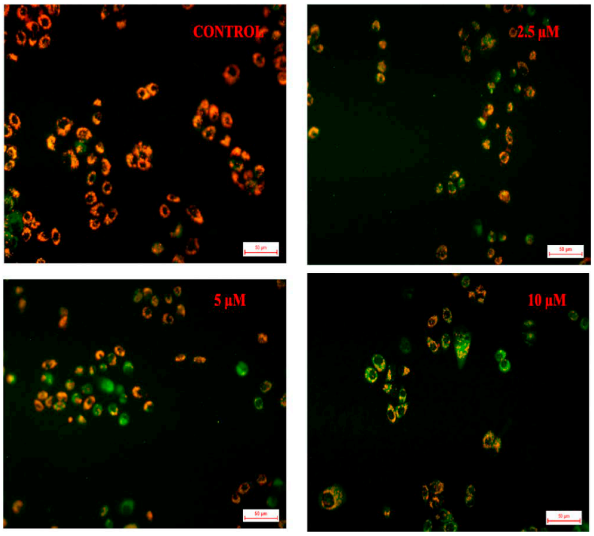
NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3-25), 1.02 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.19 (s, 3H, CH_3-26), 1.37–1.57 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.53 (s, 3H, CH_3-27), 1.60 (s, 3H, CH_3-28), 1.61 (s, 3H, CH_3-29), 1.90–2.26 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.39 (m, 1H, CH-2), 2.60 (m, 1H, CH-2), 4.38 (s, 2H, —CH_2N—), 5.11 (t, 1H, J = 6.86 Hz, CH-13), 5.17 (t, 1H, J = 7.17 Hz, CH-17), 5.35 (t, 1H, J = 7.01 Hz, CH-21), 6.85 (Brs, 1H, —CH or imidazole ring proton), 7.04 (Brs, 1H, —CH or imidazole ring protons), 7.45 (Brs, 1H, —CH or imidazole ring protons). ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.80 (C_3), 137.17 (imidazole ring-C), 135.24 (C_{14}), 134.11 (C_{18}), 130.13 (C_{22}), 129.70 (C_{21}), 128.94 (imidazole -C), 124.80 (C_{13}), 124.74 (C_{17}), 119.00 (imidazole ring-C), 73.46 (C_8), 60.27 (C_9), 55.11 (C_{30}), 55.06 (C_5), 47.15 (C_4), 43.74 (C_7), 39.58 (C_{19}), 38.95 (C_{10}), 38.53 (C_1), 38.27 (C_{15}), 33.90 (C_2), 31.10 (C_{12}), 26.54 (C_{20}), 26.31 (C_6), 26.21 (C_{16}), 25.70 (C_{11}), 23.57 (C_{26}), 21.31 ($C_{23,}$ C_{24}), 16.18 (C_{27}), 15.87 (C_{28}), 14.78 (C_{25}), 13.90 (C_{29}); ESI-HRMS Calcd for $C_{33}H_{53}O_2N_2$ $[M+H]^+$ 509.4091, found 509.4101.

4.1.4.2. (5S,8R,9R,10S)-8-hydroxy-30-(piperidin-1-yl) polypoda-13E,-17E,21E-triene-3-one ***(4b)***. Yield 57%; light yellow semi solid; R_f = 0.42 (50% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3445, 2927, 2855, 1703, 1636, 1455, 1383, 1267, 1118, 1081, 766; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3-25), 1.00 (s, 3H, CH_3-24), 1.07 (s, 3H, CH_3-23), 1.17 (s, 3H, CH_3-26), 1.42–1.60 (m, 12H, CH-9, CH_2-11, CH_2-6, CH-5, —$(CH_2)_3$), 1.58 (s, 6H, CH_3-27, CH_3-28), 1.63 (s, 3H, CH_3-29), 1.88–2.20 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.32 (m, 4H, —N$(CH_2)_2$ or piperidine ring protons), 2.38 (m, 1H, CH-2), 2.57 (m, 1H, CH-2), 2.83 (s, 2H, sbndCH2N—), 5.08 (t, 1H, J = 7.01 Hz, CH-13), 5.14 (t, 1H, J = 7.01 Hz, CH-17), 5.25 (t, 1H, J = 6.86 Hz, CH-21). ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.81 (C_3), 135.40 (C_{14}), 134.70 (C_{18}), 131.79 (C_{22}), 128.33 (C_{21}), 124.62 (C_{13}), 124.30 (C_{17}), 73.56 (C_8), 67.81 (C_{30}), 60.26 (C_9), 55.09 (C_5), 54.18 (—N $(CH_2)_2$ or 2 × piperidine ring-C), 47.44 (C_4), 43.77 (C_7), 39.62 (C_{19}), 39.38 (C_{10}), 38.54 (C_1), 38.25 (C_{15}), 33.90 (C_2), 31.11 (C_{12}), 26.57 (C_{20}), 26.36 (C_6), 26.24 (C_{16}), 25.72 (C_{11}), 25.55 ((—CH_2)$_2$ or 2 ×



(4b, MCF-7)

(9d, HT-29)



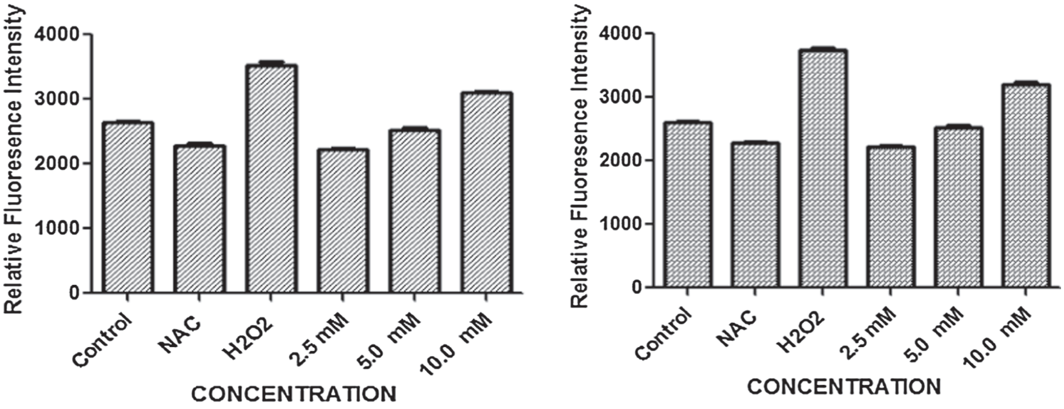
(9i, DU145)

Fig. 6. Compounds **4b, 9d** and **9i** induced loss of mitochondrial membrane potential (ΔΨm) in MCF-7, HT-29 and DU145 cells analyzed using lipophilic cationic florescent JC-1 dye staining, after treated with different concentrations (2.5 µM, 5 µM and 10 µM) for 24 h. Cells staining orange (JC-1 aggregates) have a healthy ΔΨm, while cells staining green (JC-1 monomers) are cells with a disrupted ΔΨm.

piperidine ring-C), 24.33 ((−CH_2) or piperidine ring-C), 23.57 (C_{26}), 21.30 ($C_{23,}$ C_{24}), 16.19 (C_{27}), 15.92 (C_{28}), 15.20 (C_{25}), 14.78 (C_{29}); ESI-HRMS Calcd for $C_{35}H_{60}O_2N$ [M + H]$^+$ 526.4600, found 526.4618.

*4.1.4.3. (5S,8R,9R,10S)-8-hydroxy-30-(morpholino-1-yl) polypoda-13E,17E,21E-triene-3-one (**4c**)*. Yield 73%; light yellow semi solid; R_f = 0.46 (40% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3467, 2928, 2856, 1704, 1454, 1384, 1268, 1117, 1076, 926, 866, 761, 590; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.08 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.43–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.58 (s, 6H, CH_3-27, CH_3-28), 1.62 (s, 3H, CH_3-29), 1.67 (m, 2H, CH_2-7), 1.88–2.20 (m, 12H, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.35 (m, 5H, CH-2, −$N(CH_2)_2$ or morpholine ring protons), 2.57 (m, 1H, CH-2), 2.83 (s, 2H, −CH_2N−), 3.68 (t, 4H, *J* = 4.57 Hz, −$O(CH_2)_2$ or morpholine ring protons), 5.08 (t, 1H, *J* = 7.17 Hz, CH-13), 5.15 (t, 1H, *J* = 7.17 Hz, CH-17), 5.26 (t, 1H, *J* = 6.86 Hz, CH-21). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.86 (C_3), 135.40 (C_{14}), 134.64 (C_{18}), 131.37 (C_{22}), 128.49 (C_{21}), 124.63 (C_{13}), 124.37 (C_{17}), 73.57 (C_8), 67.73 (C_{30}), 66.93 (−$O(CH_2)_2$ or 2 × morpholine ring-C), 60.27 (C_9), 55.08 (C_5), 53.40 (−$N(CH_2)_2$ or 2 × morpholine ring-C), 47.40 (C_4), 43.73 (C_7), 39.62 (C_{19}), 39.38 (C_{10}), 38.53 (C_1), 38.25 (C_{15}), 33.90 (C_2), 31.11 (C_{12}), 26.59 (C_{20}), 26.28 (C_6), 26.23 (C_{16}), 25.70 (C_{11}), 23.56 (C_{26}), 21.30 ($C_{23,}$ C_{24}), 16.19 (C_{27}), 15.90 (C_{28}), 15.01 (C_{25}), 14.78 (C_{29}); ESI-HRMS Calcd for $C_{34}H_{58}O_3N$ [M+H]$^+$ 528.4414, found 528.4411.

*4.1.4.4. (5S,8R,9R,10S)-8-hydroxy-30-(thiomorpholino-1-yl) polypoda-13E,17E,21E-triene-3-one (**4d**)*. Yield 78%; light yellow semi solid; R_f = 0.46 (40% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3456, 2926, 2855, 1737, 1706, 1458, 1384, 1272, 1182, 1079, 927, 771, 590; ^1H NMR (500 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.44–1.54 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.60 (s, 9H, CH_3-27, CH_3-28, CH_3-29), 1.80–2.18 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.40 (m, 1H, CH-2), 2.63 (m, 9H, CH-2, −$S(CH_2)_2$ or thiomorpholine ring protons, −$N(CH_2)_2$ or thiomorpholine ring protons), 2.82 (s, 2H, −CH_2N−), 5.09 (t, 1H, *J* = 7.33 Hz, CH-13), 5.15 (t, 1H, *J* = 6.48 Hz, CH-17), 5.25 (t, 1H, *J* = 6.40 Hz, CH-21). ^{13}C NMR (100 MHz, $CDCl_3$):



(4b, MCF-7) (9d, HT-29)

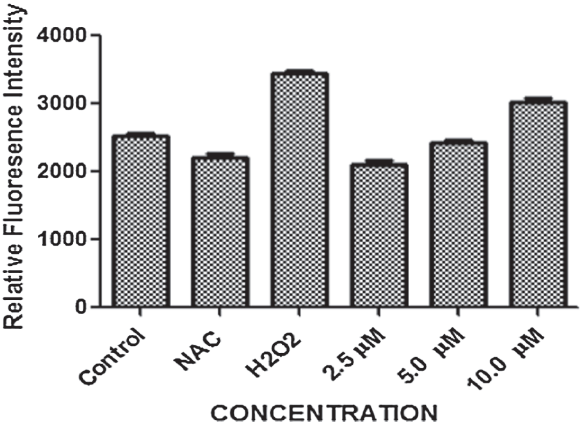


Fig. 7. Effect of compounds **4b, 9d** and **9i** on intracellular Reactive Oxygen Species levels (ROS). MCF-7, HT-29 and DU145 cells were treated with different concentrations (2.5 μM, 5 μM and 10 μM) of compounds **4b, 9d and 9i** and stained with DCFDA. Images were captured by fluorescence microscope (Nikon).

δ 216.84 (C_3), 135.46 (C_{14}), 134.69 (C_{18}), 131.80 (C_{22}), 128.21 (C_{21}), 124.63 (C_{13}), 124.37 (C_{17}), 73.61 (C_8), 67.90 (C_{30}), 60.29 (C_9), 55.09 (C_5), 54.72 (-$N(CH_2)_2$ or 2 × thiomorpholine ring-C), 47.36 (C_4), 43.79 (C_7), 39.65 (C_{19}), 39.40 (C_{10}), 38.55 (C_1), 38.26 (C_{15}), 33.92 (C_2), 31.13 (C_{12}), 27.95 ($-S(CH_2)_2$ or 2 × thiomorpholine ring-C), 26.61 (C_{20}), 26.31 (C_6), 26.25 (C_{16}), 25.71 (C_{11}), 23.59 (C_{26}), 21.32 ($C_{23,}$ C_{24}), 16.22 (C_{27}), 15.92 (C_{28}), 14.94 (C_{25}), 14.80 (C_{29}); ESI-HRMS Calcd for $C_{34}H_{58}O_2NS$ $[M+H]^+$ 544.4192, found 544.4182.

4.1.5. General procedure for the synthesis of compounds (6a-6d)

To a stirred solution of compound **3** (100 mg, 0.19 mmol) in dry DMF (2 mL) NaN_3 (28 mg, 0.43 mmol) was added**.** The resulting mixture was stirred at 50 °C for 3 h. After completion of reaction, it was extracted with ethyl acetate (3 × 10 mL)). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and concentrated to obtain the crude product. The crude product was purified by column chromatography with *n*-hexane:ethyl acetate (90:10 v/v) to yield the pure compound (**5**) in 42% yield. Further, to the stirred solution of compound **5** (50 mg, 0.10 mmol) in THF: H_2O (1:1), substituted phenyl acetylene (0.18 mmol), $CuSO_4 \cdot 5H_2O$ (23 mg, 0.92 mmol) and sodium ascorbate (20 mg, 0.10 mmol) were added and the resulting mixture was stirred at room temperature for 12 h. After completion of the reaction, it was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography with *n*-hexane:ethyl acetate (90:10 to 60:40 v/v) to afford the desired pure compounds in 50–67% yield.

*4.1.5.1. (5S,8R,9R,10S)-8-hydroxy-30-(4-phenyl-1H-1,2,3-triazol-1-yl) polypoda-13E,17E, 21E-triene-3-one (**6a**).* Yield 62%; light yellow semi solid; $R_f = 0.57$ (30% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3448, 2925, 2856, 1701, 1646, 1456, 1382, 1219, 1127, 1078, 917, 762, 695, 522; ^1H NMR (500 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.42–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.60 (s, 3H, CH_3-27), 1.61 (s, 3H, CH_3-28), 1.68 (s, 3H, CH_3-29), 1.89–2.22 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.39 (m, 1H, CH-2), 2.58 (m, 1H, CH-2), 4.97 (t, 1H, $J = 7.78$ Hz, CH-13), 5.07 (s, 2H, $-CH_2N-$), 5.11 (t, 1H, $J = 6.86$ Hz, CH-17), 5.16 (t, 1H, $J = 6.86$ Hz, CH-21), 7.32 (t, 2H, $J = 7.32$ Hz, Ar-H), 7.42 (t, 2H, $J = 7.62$ Hz, Ar-H), 7.71 (Brs, 1H, $-NCH-$ or triazole ring proton), 7.85 (d, 1H, $J = 7.32$ Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.85 (C_3), 147.50 (triazole ring-C), 142.63 (Ar-C), 135.17 (C_{14}), 133.05 (C_{18}), 130.68 (C_{22}), 128.76 (2 × Ar-C), 128.03 (C_{21}), 125.82 (C_{13}), 125.60 (2 × Ar-C), 124.85 (C_{17}), 118.32 (triazole ring-C), 114.63 (Ar-C), 73.60 (C_8), 65.79 (C_{30}), 60.31 (C_9), 55.09 (C_5), 47.46 (C_4), 43.75 (C_7), 39.48 (C_{19}), 38.54 (C_1), 38.27 (C_{15}), 35.78 (C_{10}), 33.92 (C_2), 31.14 (C_{12}), 26.50 (C_{20}), 26.24 (C_{16}), 25.70 (C_{11}), 23.58 (C_{26}), 21.30 ($C_{23,}$ C_{24}), 19.01 (C_6), 16.16 (C_{27}), 15.92 (C_{28}), 14.79 (C_{25}, C_{29}); ESI-HRMS Calcd for $C_{38}H_{56}O_2N_3$ $[M+H]^+$ 586.4345, found 586.4367.

*4.1.5.2. (5S,8R,9R,10S)-8-hydroxy-30-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)polypoda-13E,17E,21E-triene-3-one (**6b**).* Yield 50%; light yellow semi solid; $R_f = 0.57$ (30% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3451, 2924, 2854, 1702, 1560, 1457, 1384, 1226, 1155, 1077, 972, 840, 746, 603, 524; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3-25), 1.00 (s, 3H, CH_3-24), 1.08 (s, 3H, CH_3-23), 1.17 (s, 3H, CH_3-26), 1.41–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.58 (s, 6H, CH_3-27, CH_3-28), 1.60 (s, 3H, CH_3-29), 1.88–2.20 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.38 (m, 1H, CH-2), 2.57 (m, 1H,

Table 2
Anti-inflammatory results of synthesized compounds (**2-10d**).

Compounds	% Inhibition at (20 μM)		
	TNF-α	IL-1β	% Cell viability
1	66.80 ± 2.73	23.25 ± 7.32	91.80 ± 4.36
2	75.34 ± 2.32	58.28 ± 0.30	91.66 ± 1.08
4a	68.69 ± 0.12	9.93 ± 2.15	85.92 ± 4.22
4b	NA	15.67 ± 5.23	85.36 ± 2.15
4c	47.26 ± 1.91	37.56 ± 5.62	90.41 ± 0.90
4d	NA	18.33 ± 0.69	100.51 ± 2.53
6a	25.99 ± 3.02	44.56 ± 5.52	96.60 ± 2.67
6b	32.15 ± 2.09	47.81 ± 3.41	100.45 ± 4.02
6c	8.14 ± 2.37	36.57 ± 1.46	100.12 ± 2.52
6d	NA	46.68 ± 4.90	100.21 ± 4.77
7a	NA	37.65 ± 2.15	89.62 ± 1.76
7b	18.82 ± 4.04	45.60 ± 1.27	88.47 ± 1.97
7c	NA	30.29 ± 2.67	91.88 ± 1.99
8	27.12 ± 0.93	40.59 ± 4.55	99.96 ± 3.37
9a	61.56 ± 1.41	12.69 ± 1.23	85.19 ± 3.25
9b	99.03 ± 2.82	7.36 ± 1.78	99.22 ± 1.09
9c	83.96 ± 5.97	54.67 ± 4.97	100.23 ± 1.22
9d	NA	19.82 ± 4.13	88.14 ± 1.54
9e	30.86 ± 0.19	36.43 ± 4.49	105.61 ± 5.79
9f	60.96 ± 1.94	10.07 ± 8.10	92.89 ± 0.86
9g	68.37 ± 0.12	41.72 ± 3.88	75.06 ± 4.06
9h	78.73 ± 1.34	37.61 ± 2.70	90.21 ± 5.93
9i	76.11 ± 1.70	48.40 ± 1.80	88.05 ± 0.34
9j	44.52 ± 0.74	44.29 ± 5.66	84.83 ± 2.91
9k	29.37 ± 4.40	47.04 ± 4.49	97.03 ± 3.66
9l	NA	48.13 ± 3.38	86.17 ± 0.76
9m	21.60 ± 1.01	34.94 ± 4.67	95.80 ± 3.51
10a	NA	17.25 ± 0.07	84.15 ± 1.24
10b	NA	16.48 ± 2.06	82.40 ± 1.82
10c	NA	28.44 ± 0.21	94.32 ± 5.35
10d	NA	20.90 ± 1.87	89.57 ± 2.74
Prednisolone (1 μM)	79.37 ± 1.08	77.34 ± 0.46	96.78 ± 2.73

Table 3
IC_{50} (μM) values of potent anti-inflammatory compounds.

Compounds	IC_{50} (μM)	
	TNF-α	IL-1β
1	21.25 ± 1.47	24.36 ± 1.12
2	**9.39 ± 0.44**	**12.15 ± 1.36**
4a	15.34 ± 1.04	40.96 ± 1.20
8	36.87 ± 2.06	24.63 ± 1.56
9a	20.23 ± 1.23	38.01 ± 2.06
9b	12.65 ± 1.20	47.17 ± 2.7
9c	**10.02 ± 2.13**	23.65 ± 1.48
9f	11.41 ± 0.46	45.19 ± 1.78
9g	**10.53 ± 0.48**	49.96 ± 2.07
9h	13.15 ± 0.47	38.09 ± 1.99
9i	11.78 ± 1.60	31.41 ± 2.17

CH-2), 4.86 (s, 2H, $-CH_2N-$), 5.13 (m, 2H, CH-13, CH-17), 5.52 (t, 1H, $J = 7.09$ Hz, CH-21), 7.09 (m, 2H, Ar-H), 7.65 (Brs, 1H, −NCH− or triazole ring proton), 7.78 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.85 (C_3), 163.77 (Ar-C), 147.03 (triazole ring-C), 135.26 (C_{14}), 134.10 (C_{18}), 131.34 ($C_{22,}$ Ar-C), 129.28 (C_{21}), 127.38 (Ar-C), 127.30 (Ar-C), 124.85 (C_{13}), 124.72 (C_{17}), 118.80 (triazole ring-C), 115.81 (Ar-C), 115.60 (Ar-C), 73.60 (C_8), 60.25 (C_9), 58.43 (C_{30}), 55.07 (C_5), 47.45 (C_4), 43.75 (C_7), 39.60 (C_{19}), 38.86 (C_{10}), 38.52 (C_1), 38.25 (C_{15}), 33.90 (C_2), 31.11 (C_{12}), 26.60 (C_{20}), 26.31 (C_6), 26.20 (C_{16}), 25.70 (C_{11}), 23.55 (C_{26}), 21.28 ($C_{23,}$ C_{24}), 16.15 (C_{27}), 15.90 (C_{28}), 14.76 (C_{25}), 14.00 (C_{29}); ESI-HRMS Calcd for $C_{38}H_{55}O_2N_3F$ $[M+H]^+$ 604.4277, found 604.4272.

*4.1.5.3. (5S,8R,9R,10S)-8-hydroxy-30-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)polypoda-13E,17E,21E-triene-3-one **(6c)***. Yield 56%; light yellow semi solid; $R_f = 0.57$ (30% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3450, 2925, 2855, 1700, 1455, 1384, 1268, 1224, 1087, 972, 832, 760, 723, 515; ^1H NMR (500 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.08 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.42–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.58 (s, 6H, CH_3-27, CH_3-28), 1.60 (s, 3H, CH_3-29), 1.66 (m, 2H, CH_2-7), 1.88–2.20 (m, 12H, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.38 (m, 1H, CH-2), 2.58 (m, 1H, CH-2), 4.87 (s, 2H, $-CH_2N-$), 5.13 (m, 2H, CH-13, CH-17), 5.52 (t, 1H, $J = 7.17$ Hz, CH-21), 7.38 (d, 2H, $J = 8.54$ Hz, Ar-H), 7.68 (Brs, 1H, −NCH− or triazole ring proton), 7.76 (d, 2H, $J = 8.54$ Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.81 (C_3), 146.86 (triazole ring-C), 135.27 (C_{14}), 134.10 (C_{18}), 133.74 (Ar-C), 131.43 (C_{22}), 129.25 (C_{21}), 129.18 (Ar-C), 128.94 (2Ar-C), 126.88 (2Ar-C), 124.88 (C_{13}), 124.75 (C_{17}), 119.12 (triazole ring-C), 73.60 (C_8), 60.28 (C_9), 58.46 (C_{30}), 55.10 (C_5), 47.45 (C_4), 43.80 (C_7), 39.61 (C_{19}), 38.87 (C_{10}), 38.54 (C_1), 38.27 (C_{15}), 33.91 (C_2), 31.12 (C_{12}), 26.61 (C_{20}), 26.34 (C_6), 26.23 (C_{16}), 25.70 (C_{11}), 23.60 (C_{26}), 21.30 ($C_{23,}$ C_{24}), 16.17 (C_{27}), 15.92 (C_{28}), 14.80 (C_{25}), 14.01 (C_{29}); ESI-HRMS Calcd for $C_{38}H_{55}O_2N_3{}^{35}Cl$ $[M+H]^+$ 620.3968, found 620.3977, Isotopic peak Calcd for $C_{38}H_{55}O_2N_3{}^{37}Cl$ $[M+H]^+$ 621.3995.

*4.1.5.4. (5S,8R,9R,10S)- 8-hydroxy-30-(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)polypoda-13E,17E,21E-triene-3-one **(6d)***. Yield 67%; light yellow semi solid; $R_f = 0.57$ (30% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3445, 2926, 2857, 2107, 1701, 1455, 1384, 1225, 1072, 828, 757, 513; ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.43–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.59 (s, 6H, CH_3-27, CH_3-28), 1.61 (s, 3H, CH_3-29), 1.66 (m, 2H, CH_2-7), 1.89–2.21 (m, 12H, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.39 (m, 1H, CH-2), 2.59 (m, 1H, CH-2), 4.88 (s, 2H, $-CH_2N-$), 5.13 (m, 2H, CH-13, CH-17), 5.52 (t, 1H, $J = 7.01$ Hz, CH-21), 7.54 (d, 2H, $J = 8.24$ Hz, Ar-H), 7.70 (Brs, 1H, −NCH− or triazole ring proton), 7.71 (d, 2H, $J = 8.24$ Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.80 (C_3), 146.90 (triazole ring-C), 135.29 (C_{14}), 134.10 (C_{18}), 131.90 (2 × Ar-C), 131.44 (C_{22}), 129.63 (Ar-C), 129.25 (C_{21}), 127.18 (2 × Ar-C), 124.90 (C_{13}), 124.75 (C_{17}), 121.90 (Ar-C), 119.14 (triazole ring-C), 73.61 (C_8), 60.28 (C_9), 58.47 (C_{30}), 55.11 (C_5), 47.46 (C_4), 43.80 (C_7), 39.62 (C_{19}), 38.87 (C_{10}), 38.54 (C_1), 38.28 (C_{15}), 33.92 (C_2), 31.12 (C_{12}), 26.62 (C_{20}), 26.34 (C_6), 26.24 (C_{16}), 25.70 (C_{11}), 23.60 (C_{26}), 21.30 ($C_{23,}$ C_{24}), 16.18 (C_{27}), 15.92 (C_{28}), 14.79 (C_{25}), 14.01 (C_{29}); ESI-HRMS Calcd for $C_{38}H_{54}O_2N_3{}^{79}Br$ $[M+Na]^+$ 686.3299, found 686.3291, Isotopic peak Calcd for $C_{38}H_{54}O_2N_3{}^{81}Br$ $[M+Na]^+$ 688.3283.

4.1.6. General procedure for the synthesis of compounds (7a-7c)

To a solution of compound **1** (50 mg, 0.10 mmol) in dry DCM (2 mL) were added successively anhydrous pyridine (21 mg, 0.26 mmol) and acyl chloride (1 mmol). The resultant mixture was stirred at room temperature for 4 h (monitored by TLC analysis). After completion of the reaction, it was extracted with DCM (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography with *n*-hexane:ethyl acetate (90:10 v/v) to provide the pure compounds in 80–88% yield.

*4.1.6.1. (5S,8R,9R,10S)-3-oxo-8-hydroxypolypoda-13E,17E,21E-triene-30–1-yl acetate **(7a)***. Yield 84%; light yellow semi solid; $R_f = 0.62$ (20% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3452, 2928, 2860, 1735, 1707, 1452, 1380, 1233, 1122, 1020, 841, 769, 592; ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.42–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.59 (s, 6H, CH_3-27, CH_3-28), 1.63 (s, 3H, CH_3-29), 1.88–2.16 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.06 (s, 3H, $-COCH_3$), 2.38 (m, 1H, CH-2), 2.58 (m, 1H, CH-2), 4.43 (s, 2H, $-CH_2O-$), 5.10 (t, 1H, $J = 6.86$ Hz, CH-13), 5.15 (t, 1H, $J = 7.01$ Hz, CH-17), 5.43 (t, 1H, $J = 7.01$ Hz, CH-21). ^{13}C NMR

(125 MHz, $CDCl_3$): δ 216.90 (C_3), 171.05 (−CH_2CO−), 135.39 (C_{14}), 134.40 (C_{18}), 129.84 (C_{21}), 129.62 (C_{22}), 124.66 (C_{13}), 124.58 (C_{17}), 73.60 (C_8), 70.39 (C_{30}), 60.31 (C_9), 55.08 (C_5), 47.46 (C_4), 43.76 (C_7), 39.59 (C_{19}), 38.89 (C_{10}), 38.55 (C_1), 38.25 (C_{15}), 33.92 (C_2), 31.15 (C_{12}), 26.54 (C_{20}), 26.26 (C_6), 26.24 (C_{16}), 25.72 (C_{11}), 23.54 (C_{26}), 21.30 ($C_{23,}$ C_{24}), 21.01 (−$COCH_3$), 16.16 (C_{27}), 15.93 (C_{28}), 14.79 (C_{25}), 13.94 (C_{29}); ESI-HRMS Calcd for $C_{32}H_{52}O_4Na$ $[M+Na]^+$ 523.3758, found 523.3732.

*4.1.6.2. (5S,8R,9R,10S)-3-oxo-8-hydroxypolypoda-13E,17E,21E-triene-30–1-yl propionate (**7b**)*. Yield 88%; light yellow semi solid; R_f = 0.66 (20% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3456, 2926, 2855, 1737, 1706, 1458, 1384, 1272, 1182, 1080, 927, 771, 590; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 1.02 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.14 (t, 1H, J = 7.58 Hz, Aliphatic chain-CH_3), 1.19 (s, 3H, CH_3-26), 1.42–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.59 (s, 6H, CH_3-27, CH_3-28), 1.64 (s, 3H, CH_3-29), 1.88–2.16 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.34 (q, 2H, J = 7.58 Hz, −$COCH_2$−), 2.39 (m, 1H, CH-2), 2.59 (m, 1H, CH-2), 4.45 (s, 2H, −CH_2O−), 5.10 (t, 1H, J = 6.72 Hz, CH-13), 5.16 (t, 1H, J = 7.09 Hz, CH-17), 5.43 (t, 1H, J = 6.84 Hz, CH-21). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.02 (C_3), 174.50 (CH_2CO−), 135.42 (C_{14}), 134.43 (C_{18}), 129.46 ($C_{21,}$ C_{22}), 124.71 (C_{13}), 124.60 (C_{17}), 73.63 (C_8), 70.22 (C_{30}), 60.33 (C_9), 55.11 (C_5), 47.50 (C_4), 43.75 (C_7), 39.62 (C_{19}), 39.04 (C_{10}), 38.57 (C_1), 38.28 (C_{15}), 33.97 (C_2), 31.21 (C_{12}), 27.63 (−$COCH_2$−), 26.55 (C_{20}), 26.35 (C_6), 26.25 (C_{16}), 25.74 (C_{11}), 23.56 (C_{26}), 21.35 ($C_{23,}$ C_{24}), 16.20 (C_{27}), 15.97 (C_{28}), 14.83 (C_{25}), 13.96 (C_{29}), 9.19 (−$COCH_2$−CH_3); ESI-HRMS Calcd for $C_{33}H_{54}O_4$ $[M+Na]^+$ 537.3902, found 537.3914.

*4.1.6.3. (5S,8R,9R,10S)-3-oxo-8-hydroxypolypoda-13E,17E,21E-triene-30–1-yl butyrate (**7c**)*. Yield 80%; light yellow semi solid; R_f = 0.70 (20% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3452, 2926, 2855, 1734, 1708, 1457, 1383, 1264, 1176, 1081, 966, 926, 756; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 0.94 (t, 3H, J = 7.33 Hz, Aliphatic chain-CH_3),1.01 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.19 (s, 3H, CH_3-26), 1.43–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.59 (s, 6H, CH_3-27, CH_3-28), 1.64 (s, 3H, CH_3-29), 1.65 (m, 2H, Aliphatic chain-CH_2), 1.88–2.18 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.30 (t, 2H, J = 7.33 Hz, −$COCH_2$−), 2.40 (m, 1H, CH-2), 2.59 (m, 1H, CH-2), 4.44 (s, 2H, −CH_2O−), 5.10 (t, 1H, J = 6.72 Hz, CH-13), 5.15 (t, 1H, J = 7.33 Hz, CH-17), 5.43 (t, 1H, J = 6.96 Hz, CH-21). ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.60 (C_3), 173.51 (CH_2CO−), 135.40 (C_{14}), 134.43 (C_{18}), 129.33 ($C_{21,}$ C_{22}), 124.77 (C_{13}), 124.65 (C_{17}), 73.61 (C_8), 70.01 (C_{30}), 60.38 (C_9), 55.23 (C_5), 47.46 (C_4), 43.92 (C_7), 39.64 (C_{19}), 39.06 (C_{10}), 38.64 (C_1), 38.38 (C_{15}), 36.30 (−$COCH_2$−), 33.93 (C_2), 31.15 (C_{12}), 26.65 (C_{20}), 26.40 (C_6), 26.37 (C_{16}), 25.80 (C_{11}), 23.65 (C_{26}), 21.43 (C_{23}), 21.32 (C_{24}), 18.49 (−CH_2CH_3), 16.17 (C_{27}), 15.96 (C_{28}), 14.80 (C_{25}), 13.90 (C_{29}), 13.64 (−CH_2CH_3); ESI-HRMS Calcd for $C_{34}H_{56}O_4$ $[M+Na]^+$ 551.4064, found 551.4070.

4.1.7. General procedure for the synthesis of compounds (9a-9m)

To a solution of compound **8** (50 mg, 0.10 mmol) in dry DCM (2 mL), EDCI (12 mg, 0.07 mmol), HOBT (18 mg, 0.11 mmol), N, N diisopropylethylamine (15 mg, 0.12 mmol) and appropriative amine (0.5 mmol) were added successively at room temperature. The resultant mixture was stirred at room temperature for 12 h (monitored by TLC analysis). After completion of the reaction, it was washed with saturated $NaHCO_3$ solution and extracted with more DCM (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography with *n*-hexane:ethyl acetate (60:40 to 40:60 v/v) as eluent to furnish the pure compounds in 60–83% yield.

*4.1.7.1. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-N-methyl-polypoda-13E,17E,21E-trienamide (**9a**)*. Yield 69%; light yellow semi solid; R_f = 0.50 (60% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3380, 2933, 2869, 1701, 1619, 1536, 1452, 1382, 1280, 1128, 1012, 926, 758, 590; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.28–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.60 (s, 6H, CH_3-27, CH_3-28), 1.82 (s, 3H, CH_3-29), 1.88–2.24 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.38 (m, 1H, CH-2), 2.58 (m, 1H, CH-2), 2.85 (d, 3H, J = 4.73 Hz, N-CH_3), 5.13 (m, 2H, CH-13, CH-17), 5.78 (Brs, 1H, −NH−), 6.27 (t, 1H, J = 7.17 Hz, CH-21). ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.88 (C_3), 170.10 (C_{30}), 135.43 (C_{21}), 135.11 (C_{18}), 133.92 (C_{14}), 130.71 (C_{22}), 124.88 (C_{13}), 124.82 (C_{17}), 73.51 (C_8), 60.23 (C_9), 55.10 (C_5), 47.43 (C_4), 43.68 (C_7), 39.50 (C_{19}), 38.51 (C_{10}), 38.41 (C_1), 38.26 (C_{15}), 33.90 (C_2), 31.07 (C_{12}), 26.71 (C_{20}), 26.50 (−NCH_3−), 26.41 (C_6), 26.15 (C_{16}), 25.65 (C_{11}) 23.54 (C_{26}), 21.28 ($C_{23,}$ C_{24}), 16.12 (C_{27}), 15.92 (C_{28}), 14.76 (C_{25}), 12.69 (C_{29}); ESI-HRMS Calcd for $C_{31}H_{51}O_3N$ $[M+Na]^+$ 508.3742, found 508.3761.

*4.1.7.2. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-N-ethyl-polypoda-13E,17E,21E-trienamide (**9b**)*. Yield 74%; light yellow semi solid; R_f = 0.53 (40% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3398, 2931, 2862, 1701, 1622, 1533, 1450, 1382, 1135, 1081, 925, 759, 590; ^1H NMR (500 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.08 (s, 3H, CH_3-23), 1.15 (t, 3H, J = 7.17 Hz, −CH3), 1.18 (s, 3H, CH_3-26), 1.24–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.59 (s, 6H, CH_3-27, CH_3-28), 1.82 (s, 3H, CH_3-29), 1.86–2.23 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.38 (m, 1H, CH-2), 2.58 (m, 1H, CH-2), 3.33 (m, 2H, −NCH_2−), 5.13 (m, 2H, CH-13, CH-17), 5.72 (Brs, 1H, −NH−), 6.26 (t, 1H, J = 7.17 Hz, CH-21). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.86 (C_3), 169.30 (C_{30}), 135.26 (C_{21}), 135.13 (C_{18}), 133.97 (C_{14}), 130.90 (C_{22}), 124.87 (C_{13}), 124.82 (C_{17}), 73.50 (C_8), 60.23 (C_9), 55.10 (C_5), 47.44 (C_4), 43.68 (C_7), 39.52 (C_{19}), 38.51 (C_{10}), 38.43 (C_1), 38.27 (C_{15}), 34.50 (−NCH_2−), 33.91 (C_2), 31.08 (C_{12}), 26.76 (C_{20}), 26.45 (C_6), 26.22 (C_{16}), 25.65 (C_{11}), 23.55 (C_{26}), 21.28 ($C_{23,}$ C_{24}), 16.13 (C_{27}), 15.92 (C_{28}), 14.83 (C_{25}), 14.78 (−NCH_3), 12.70 (C_{29}); ESI-HRMS Calcd for $C_{32}H_{53}O_3N$ $[M+Na]^+$ 522.3894, found 522.3917.

*4.1.7.3. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-N-propyl-polypoda-13E,17E,21E-trienamide (**9c**)*. Yield 72%; light yellow semi solid; R_f = 0.57 (40% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3412, 2924, 2854, 1702, 1621, 1530, 1458, 1383, 1281, 1131, 1079, 925, 770; ^1H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, 3H, J = 7.45 Hz, −CH_3), 0.95 (s, 3H, CH_3-25), 1.02 (s, 3H, CH_3-24), 1.10 (s, 3H, CH_3-23), 1.20 (s, 3H, CH_3-26), 1.42–1.57 (m, 8H, CH-9, CH_2-11, CH_2-6, CH-5, −CH_2−), 1.60 (s, 6H, CH_3-27, CH_3-28), 1.84 (s, 3H, CH_3-29), 1.90–2.26 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.40 (m, 1H, CH-2), 2.60 (m, 1H, CH-2), 3.27 (q, 2H, J = 7.01 Hz, −NCH_2−), 5.15 (m, 2H, CH-13, CH-17), 5.75 (Brs, 1H, −NH−), 6.28 (t, 1H, J = 7.10 Hz, CH-21). ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.90 (C_3), 169.44 (C_{30}), 135.24 (C_{21}), 135.11 (C_{18}), 133.95 (C_{14}), 130.92 (C_{22}), 124.85 (C_{13}), 124.80 (C_{17}), 73.51 (C_8), 60.21 (C_9), 55.07 (C_5), 47.43 (C_4), 43.63 (C_7), 41.34 (−NCH_2−), 39.51 (C_{19}), 38.50 (C_{10}), 38.42 (C_1), 38.23 (C_{15}), 33.91 (C_2), 31.08 (C_{12}), 26.73 (C_{20}), 26.43 (C_6), 26.17 (C_{16}), 25.63 (C_{11}), 23.51 (C_{26}), 22.80 (−NCH_2-CH_2−), 21.27 ($C_{23,}$ C_{24}), 16.12 (C_{27}), 15.90 (C_{28}), 14.76 (C_{25}), 12.72 (C_{29}), 11.36 (−N−CH_2−CH_2−CH_3); ESI-HRMS Calcd for $C_{33}H_{56}O_3N$ $[M+H]^+$ 514.4252, found 514.4254.

*4.1.7.4. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-N-butyl-polypoda-13E,17E,21E-trienamide (**9d**)*. Yield 68%; light yellow semi solid; R_f = 0.56 (40% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3395, 2930, 2862, 1702, 1620, 1531, 1456, 1383, 1131, 1079, 927, 879, 753, 590; ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, 3H, J = 7.32 Hz, −CH_3), 0.93 (s, 3H, CH_3-25), 1.00 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.30–1.52 (m, 10H, CH-9, CH_2-11, CH_2-6, CH-5, −$(CH_2)_2$−), 1.58 (s, 6H, CH_3-27, CH_3-28), 1.81 (s, 3H, CH_3-29), 1.88–2.30 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.38 (m, 1H, CH-2), 2.57 (m, 1H, CH-2), 3.29 (q, 2H, J = 6.80 Hz, −NCH_2−), 5.12 (m, 2H, CH-13, CH-17), 5.72 (Brs, 1H, −NH−), 6.25 (t, 1H, J = 7.01 Hz, CH-21). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.85 (C_3), 169.42 (C_{30}), 135.19 (C_{21}), 135.14 (C_{18}), 133.98 (C_{14}), 131.00 (C_{22}), 124.90 (C_{13}), 124.82 (C_{17}), 73.52 (C_8), 60.24 (C_9), 55.11 (C_5), 47.44 (C_4), 43.70 (C_7), 39.54 (C_{19}), 39.41 (−NCH_2−), 38.52 (C_{10}), 38.44 (C_1), 38.27 (C_{15}), 33.90 (C_2), 31.68 (−N−CH_2−CH_2−), 31.08 (C_{12}), 26.76 (C_{20}), 26.48 (C_6), 26.22 (C_{16}), 25.66 (C_{11}), 23.55 (C_{26}), 21.28 ($C_{23,}$ C_{24}), 20.08 (−N−CH_2−CH_2−CH_2), 16.13 (C_{27}), 15.92 (C_{28}), 14.77 (C_{25}), 13.73 (−N−CH_2−CH_2−CH_2−CH_3), 12.72 (C_{29}); ESI-HRMS Calcd for $C_{34}H_{58}O_3N$ $[M+H]^+$ 528.4399, found 528.4411.

*4.1.7.5. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-N-pentyl-polypoda-13E,17E,21E-trienamide (**9e**)*. Yield 73%; light yellow semi solid; R_f = 0.50 (40% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3405, 2926, 2857, 1703, 1621, 1530, 1457, 1383, 1129, 1079, 926, 590; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, 3H, J = 6.86 Hz, −CH_3), 0.94 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.08 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.30–1.52 (m, 12H, CH-9, CH_2-11, CH_2-6, CH-5, −$(CH_2)_3$−), 1.59 (s, 6H, CH_3-27, CH_3-28), 1.82 (s, 3H, CH_3-29), 1.88–2.13 (m, 12H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.22 (m, 2H, CH_2-20), 2.39 (m, 1H, CH-2), 2.58 (m, 1H, CH-2), 3.28 (q, 2H, J = 7.17 Hz, −NCH_2−), 5.13 (m, 2H, CH-13, CH-17), 5.70 (Brs, 1H, −NH−), 6.26 (t, 1H, J = 7.01 Hz, CH-21). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.86 (C_3), 169.40 (C_{30}), 135.21 (C_{21}), 135.14 (C_{18}), 134.00 (C_{14}), 130.97 (C_{22}), 124.90 (C_{13}), 124.82 (C_{17}), 73.53 (C_8), 60.25 (C_9), 55.10 (C_5), 47.45 (C_4), 43.70 (C_7), 39.69 (−NCH_2−), 39.54 (C_{19}), 38.52 (C_{10}), 38.44 (C_1), 38.26 (C_{15}), 33.91 (C_2), 31.10 (C_{12}), 29.29 (−N−CH_2−CH_2−), 29.08 (-N-CH_2-CH_2-CH_2), 26.76 (C_{20}), 26.47 (C_6), 26.21 (C_{16}), 25.66 (C_{11}), 23.55 (C_{26}), 22.33 (−N−CH_2−CH_2−CH_2−), 21.29 ($C_{23,}$ C_{24}), 16.13 (C_{27}), 15.92 (C_{28}), 14.78 (C_{25}), 13.95 (−N−CH_2−CH_2−CH_2−CH_3),12.74 (C_{29}); ESI-HRMS Calcd for $C_{35}H_{59}O_3N$ $[M+Na]^+$ 564.4389, found 564.4387.

*4.1.7.6. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-(piperidin-1-yl)-polypoda-13E,17E,21E-trienamide (**9f**)*. Yield 68%; light yellow semi solid; R_f = 0.42 (40% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3419, 2927, 2856, 1704, 1609, 1445, 1382, 1276, 1219, 1123, 1080, 1015, 770, 586; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H, CH_3-25), 1.00 (s, 3H, CH_3-24), 1.07 (s, 3H, CH_3-23), 1.17 (s, 3H, CH_3-26), 1.28–1.54 (m, 8H, CH-9, CH_2-11, CH_2-6, CH-5, −CH_2), 1.58 (s, 6H, CH_3-27, CH_3-28), 1.61 (m, 4H, −$(CH_2)_2$ or piperidine ring protons), 1.79 (s, 3H, CH_3-29), 1.88–2.20 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.37 (m, 1H, CH-2), 2.57 (m, 1H, CH-2), 3.46 (Br s, 4H, −N $(CH_2)_2$ or piperidine ring protons), 5.10 (t, 1H, J = 6.71 Hz, CH-13), 5.13 (t, 1H, J = 6.40 Hz, CH-17), 5.44 (t, 1H, J = 7.01 Hz, CH-21). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.96 (C_3), 172.42 (C_{30}), 135.24 (C_{18}), 134.28 (C_{14}), 131.34 (C_{21}), 130.67 (C_{22}), 124.85 ($C_{13,}$ C_{17}), 73.51 (C_8), 60.36 (C_9), 55.13 (C_5), 47.50 (C_4), 43.72 (C_7), 43.72 (−N$(CH_2)_2$ or 2 × piperidine ring-C), 39.62 (C_{19}), 38.69 (C_{10}), 38.58 (C_1), 38.28 (C_{15}), 33.97 (C_2), 31.21 (C_{12}), 26.59 (C_{20}), 26.30 (C_6), 26.27 (−$(CH_2)_2$ or 2 X piperidine ring-C), 25.92 (C_{16}), 25.78 (−(CH_2) or piperidine ring-C), 25.71 (C_{11}), 24.67, 23.59 (C_{26}), 21.35 ($C_{23,}$ C_{24}), 16.23 (C_{27}), 15.88 (C_{28}), 14.83 (C_{25}), 14.48 (C_{29}); ESI-HRMS Calcd for $C_{35}H_{58}O_3N$ $[M+H]^+$ 540.4410, found 540.4411.

*4.1.7.7. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-(morpholino-1-yl)-polypoda-13E,17E,21E-trienamide (**9g**)*. Yield 74%; light yellow semi solid; R_f = 0.42 (40% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3450, 2924, 2855, 1703, 1619, 1456, 1451, 1383, 1275, 1115, 1076, 1030, 969, 752, 597, 554; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (s, 3H, CH_3-25), 1.02 (s, 3H, CH_3-24), 1.10 (s, 3H, CH_3-23), 1.20 (s, 3H, CH_3-26), 1.35–1.57 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.60 (s, 6H, CH_3-27, CH_3-28), 1.83 (s, 3H, CH_3-29), 1.90–2.24 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.40 (m, 1H, CH-2), 2.60 (m, 1H, CH-2), 3.57 (Br s, 4H, −N$(CH_2)_2$ or morpholine ring protons), 3.57 (Br s, 4H, −O$(CH_2)_2$ or morpholine ring protons), 5.11 (t, 1H, J = 6.86 Hz, CH-13), 5.16 (t, 1H, J = 6.86 Hz, CH-17), 5.51 (t, 1H, J = 7.01 Hz, CH-21). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.80 (C_3), 172.43 (C_{30}), 135.05 (C_{18}), 134.04 (C_{14}), 131.46 (C_{21}), 130.32 (C_{22}), 124.93 (C_{13}), 124.79 (C_{17}), 73.47 (C_8), 66.83 (−O$(CH_2)_2$ or 2 × morpholine ring-C), 60.26 (C_9), 55.05 (C_5), 47.42 (−N$(CH_2)_2$ or 2 × morpholine ring-C), 47.40 (C_4), 43.65 (C_7), 39.52 (C_{19}), 38.51 (C_{10}), 38.48 (C_1), 38.22 (C_{15}), 33.86 (C_2), 31.11 (C_{12}), 26.52 (C_{20}), 26.17 (C_6), 25.83 (C_{16}), 25.64 (C_{11}), 23.52 (C_{26}), 21.25 ($C_{23,}$ C_{24}), 16.14 (C_{27}), 15.74 (C_{28}), 14.74 (C_{25}), 14.33 (C_{29}); ESI-HRMS Calcd for $C_{34}H_{56}O_4N$ $[M+H]^+$ 542.4215, found 542.4203.

*4.1.7.8. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-(thiomorpholino-1-yl)-polypoda-13E,17E,21E-trienamide (**9h**)*. Yield 68%; light yellow semi solid; R_f = 0.52 (40% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3443, 3140, 2928, 2857, 1703, 1619, 1400, 1260, 1130, 956, 753, 585; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3-25), 1.02 (s, 3H, CH_3-24), 1.10 (s, 3H, CH_3-23), 1.20 (s, 3H, CH_3-26), 1.28–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.60 (s, 6H, CH_3-27, CH_3-28), 1.82 (s, 3H, CH_3-29), 1.90–2.23 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.40 (m, 1H, CH-2), 2.60 (m, 5H, CH-2, −S$(CH_2)_2$ or thiomorpholine ring protons), 3.80 (Br s, 4H, −N$(CH_2)_2$ or thiomorpholine ring protons), 5.12 (t, 1H, J = 6.50 Hz, CH-13), 5.16 (t, 1H, J = 6.86 Hz, CH-17), 5.48 (t, 1H, J = 7.01 Hz, CH-21). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.75 (C_3), 172.70 (C_{30}), 135.10 (C_{18}), 134.07 (C_{14}), 130.80 ($C_{22,}$ C_{21}), 124.91 (C_{13}), 124.80 (C_{17}), 74.22 (C_8), 60.31 (C_9), 55.03 (C_5), 47.46 (C_4), 47.43 (−N$(CH_2)_2$ or 2 × thiomorpholine ring-C),43.48 (C_7), 39.54 (C_{19}), 38.50 ($C_{10,}$ C_{15}), 38.24 (C_1), 33.88 (C_2), 31.12 (C_{12}), 27.70 (−S$(CH_2)_2$ or 2 × thiomorpholine ring-C), 26.55 (C_{20}), 26.20 (C_6), 25.83 (C_{16}), 25.67 (C_{11}), 23.50 (C_{26}), 21.27 ($C_{23,}$ C_{24}), 16.13 (C_{27}), 15.79 (C_{28}), 14.76 (C_{25}), 14.45 (C_{29}); ESI-HRMS Calcd for $C_{34}H_{56}O_3NS$ $[M+H]^+$ 558.3953, found 558.3953.

*4.1.7.9. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-(4-methylpiperazin-1-yl)-polypoda-13E,17E,21E-trienamide (**9i**)*. Yield 60%; light yellow semi solid; R_f = 0.40 (50% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3445, 2924, 2854, 1702, 1616, 1457, 1381, 1289, 1132, 1078, 1000, 771; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.30–1.55 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.59 (s, 6H, CH_3-27, CH_3-28), 1.80 (s, 3H, CH_3-29), 1.88–2.21 (m, 14H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16, CH_2-20), 2.30 (s, 3H, N-CH_3), 2.39 (m, 5H, CH-2, −N$(CH_2)_2$ or piperazine ring protons), 2.58 (m, 1H, CH-2), 3.80 (Br s, 4H, −N$(CH_2)_2$ or piperazine ring protons), 5.10 (t, 1H, J = 7.01 Hz, CH-13), 5.15 (t, 1H, J = 7.01 Hz, CH-17), 5.48 (t, 1H, J = 7.01 Hz, CH-21). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.82 (C_3), 172.40 (C_{30}), 135.14 (C_{18}), 134.12 (C_{14}), 131.10 (C_{21}), 130.67 (C_{22}), 124.94 (C_{13}), 124.83 (C_{17}), 73.51 (C_8), 60.32 (C_9), 55.17 (C_5), 54.84 (−N$(CH_2)_2$ or 2 × piperazine ring-C), 47.47 (−N$(CH_2)_2$ or 2 × piperazine ring-C), 47.46 (C_4), 45.73 (−NCH_3 or *N*-methyl piperazine), 43.73 (C_7), 39.57 (C_{19}), 38.58 (C_{10}), 38.54 (C_1), 38.28 (C_{15}), 33.91 (C_2), 31.88 (C_{12}), 26.55 (C_{20}), 26.24 (C_6), 25.90 (C_{16}), 25.70 (C_{11}), 23.59 (C_{26}), 21.32 ($C_{23,}$ C_{24}), 16.19 (C_{27}), 15.82 (C_{28}), 14.79 (C_{25}), 14.41 (C_{29}); ESI-HRMS Calcd for $C_{35}H_{59}O_3N_2$ $[M+H]^+$ 555.4495, found 555.4520.

*4.1.7.10. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-(N-phenyl)-polypoda-13E,17E,21E-trienamide (**9j**)*. Yield 79%; light yellow semi solid; R_f = 0.40 (30% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3442, 2926, 2856, 1699, 1664, 1599, 1530, 1440, 1384, 1317, 1247, 1127, 1078, 755, 694; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 1.02 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.43–1.56 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.60 (s, 3H, CH_3-27), 1.63 (s, 3H, CH_3-28), 1.92 (m, 2H, CH_2-7), 1.93 (s, 3H, CH_3-29), 1.98–2.13 (m, 10H, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.29 (m, 2H, CH_2-20), 2.38

(m, 1H, CH-2), 2.60 (m, 1H, CH-2), 5.16 (m, 2H, CH-13, CH-17), 6.37 (t, 1H, J = 7.01 Hz, CH-21), 7.09 (t, 1H, J = 7.47 Hz, Ar-H), 7.32 (t, 2H, J = 8.24 Hz, Ar-H), 7.55 (t, 2H, J = 7.62 Hz, Ar-H), 7.58 (Brs 1H, −NH−). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.97 (C_3), 167.68 (C_{30}), 138.05 (Ar-C), 136.12 (Ar-C), 135.11 (C_{18}), 133.83 (C_{14}), 131.85 (C_{21}), 128.87 (2Ar-C), 125.04 (C_{22}), 124.83 (C_{13}), 124.05 (C_{17}), 119.95 (2Ar-C), 73.58 (C_8), 60.15 (C_9), 55.04 (C_5), 47.46 (C_4), 43.69 (C_7), 39.49 (C_{19}), 38.48 (C_{10}), 38.35 (C_1), 38.20 (C_{15}), 33.91 (C_2), 31.02 (C_{12}), 26.87 (C_{20}), 26.37 (C_6), 26.14 (C_{16}), 25.60 (C_{11}), 23.49 (C_{26}), 21.28 ($C_{23,}$ C_{24}), 16.13 (C_{27}), 15.93 (C_{28}), 14.76 (C_{25}), 12.86 (C_{29}); ESI-HRMS Calcd for $C_{36}H_{53}O_3N$ $[M+Na]^+$ 570.3900, found 570.3917.

*4.1.7.11. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-N-(3-methoxyphenyl)-polypoda-13E,17E,21E-trienamide (**9k**)*. Yield 83%; light yellow semi solid; R_f = 0.40 (30% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3446, 2925, 2855, 1699, 1604, 1535, 1490, 1456, 1384, 1279, 1159, 1079, 963, 773, 690, 590; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3-25), 1.02 (s, 3H, CH_3-24), 1.10 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.35–1.55 (m, 8H, CH-9, CH_2-11, CH_2-6, CH-5, CH_2-7), 1.60 (s, 3H, CH_3-27), 1.63 (s, 3H, CH_3-28), 1.93 (s, 3H, CH_3-29), 1.90–2.14 (m, 10*H*, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.30 (m, 2H, CH_2-20), 2.38 (m, 1H, CH-2), 2.60 (m, 1H, CH-2), 3.81 (s, 3H, Ar-OCH_3), 5.16 (m, 2H, CH-13, CH-17), 6.36 (t, 1H, J = 6.98 Hz, CH-21), 6.66 (m, 1H, Ar-H), 6.99 (m, 1H, Ar-H), 7.21 (t, 1H, J = 8.12 Hz, Ar-H), 7.39 (t, 1H, J = 2.07 Hz, Ar-H), 7.55 (Brs, 1H, −NH−). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.86 (C_3), 167.67 (C_{30}), 160.09 (Ar-C), 139.36 (Ar-C), 136.12 (Ar-C), 135.13 (C_{18}), 133.83 (C_{14}), 131.96 (C_{21}), 129.51 (C_{22}), 125.10 (C_{13}), 124.87 (C_{17}), 111.97 (Ar-C), 110.14 (Ar-C), 105.48 (Ar-C), 73.58 (C_8), 60.20 (C_9), 55.24 (C_5), 55.09 (Ar-OCH_3), 47.47 (C_4), 43.78 (C_7), 39.51 (C_{19}), 38.52 (C_{10}), 38.37 (C_1), 38.25 (C_{15}), 33.93 (C_2), 31.04 (C_{12}), 26.90 (C_{20}), 26.41 (C_6), 26.19 (C_{16}), 25.64 (C_{11}), 23.59 (C_{26}), 21.31 ($C_{23,}$ C_{24}), 16.13 (C_{27}), 15.95 (C_{28}), 14.78 (C_{25}), 12.87 (C_{29}); ESI-HRMS Calcd for $C_{37}H_{55}O_4N$ $[M+Na]^+$ 600.4025, found 600.4023.

*4.1.7.12. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-N-(3-nitrophenyl)-polypoda-13E,17E,21E-trienamide (**9l**)*. Yield 71%; light yellow semi solid; R_f = 0.34 (30% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3441, 2925, 2855, 1781, 1702, 1640, 1456, 1384, 1263, 1082, 812, 748, 591; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (s, 3H, CH_3-25), 1.03 (s, 3H, CH_3-24), 1.10 (s, 3H, CH_3-23), 1.20 (s, 3H, CH_3-26), 1.35–1.57 (m, 8H, CH-9, CH_2-11, CH_2-6, CH-5, CH_2-7), 1.60 (s, 3H, CH_3-27), 1.63 (s, 3H, CH_3-28), 1.96 (s, 3H, CH_3-29), 1.90–2.15 (m, 10H, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.32 (m, 2H, CH_2-20), 2.39 (m, 1H, CH-2), 2.61 (m, 1H, CH-2), 5.16 (t, 2H, J = 7.01 Hz, CH-13, CH-17), 6.43 (t, 1H, J = 7.01 Hz, CH-21), 7.49 (t, 1H, J = 8.24 Hz, Ar-H), 7.94 (m, 1H, Ar-H), 8.00 (Brs, 1H, −NH−), 8.07 (m, 1H, Ar-H), 8.39 (t, 1H, J = 2.13 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.14 (C_3), 167.88 (C_{30}), 148.48 (Ar-C), 139.44 (Ar-C), 137.29 (Ar-C), 135.26 (C_{18}), 133.78 (C_{14}), 131.50 (C_{21}), 129.73 (Ar-C), 125.68 (C_{22}), 125.23 (C_{13}), 124.94 (C_{17}), 118.52 (Ar-C), 114.65 (Ar-C), 73.78 (C_8), 59.97 (C_9), 55.22 (C_5), 47.56 (C_4), 43.89 (C_7), 39.51 (C_{19}), 38.56 (C_{10}), 38.39 (C_1), 38.35 (C_{15}), 34.01 (C_2), 30.77 (C_{12}), 27.04 (C_{20}), 26.27 (C_6), 26.16 (C_{16}), 25.55 (C_{11}), 23.59 (C_{26}), 21.33 (C_{23}), 21.32 (C_{24}), 16.12 (C_{27}), 15.93 (C_{28}), 14.80 (C_{25}), 12.81 (C_{29}); ESI-HRMS Calcd for $C_{36}H_{52}O_5N_2$ $[M+Na]^+$ 615.3748, found 615.3768.

*4.1.7.13. (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-N-(3-bromophenyl)-polypoda-13E,17E,21E-trienamide (**9m**)*. Yield 60%; light yellow semi solid; R_f = 0.40 (30% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3444, 2924, 2855, 1698, 1587, 1522, 1474, 1415, 1386, 1305, 1127, 1076, 998, 868, 775, 682, 590; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3-25), 1.02 (s, 3H, CH_3-24), 1.10 (s, 3H, CH_3-23), 1.19 (s, 3H, CH_3-26), 1.35–1.47 (m, 8H, CH-9, CH_2-11, CH_2-6, CH-5, CH_2-7), 1.60 (s, 3H, CH_3-27), 1.63 (s, 3H, CH_3-28), 1.93 (s, 3H, CH_3-29), 1.90–2.14 (m, 10H, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.30 (m, 2H, CH_2-20), 2.39 (m, 1H, CH-2), 2.60 (m, 1H, CH-2), 5.15 (m, 2H, CH-13, CH-17), 6.36 (t, 1H, J = 7.17 Hz, CH-21), 7.18 (t, 1H, J = 7.93 Hz, Ar-H), 7.22 (m, 1H, Ar-H), 7.50 (m, 1H, Ar-H), 7.59 (Brs, 1H, −NH−), 7.81 (t, 1H, J = 1.83 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.06 (C_3), 167.66 (C_{30}), 139.44 (Ar-C), 136.65 (Ar-C), 135.18 (C_{18}), 133.80 (C_{14}), 131.66 (C_{21}), 130.16 (Ar-C), 126.96 (C_{22}), 125.13 (C_{13}), 124.87 (C_{17}), 122.83 (Ar-C), 122.48 (Ar-C), 118.40 (Ar-C), 73.69 (C_8), 60.11 (C_9), 55.09 (C_5), 47.50 (C_4), 43.76 (C_7), 39.48 (C_{19}), 38.51 (C_{10}), 38.32 (C_1), 38.25 (C_{15}), 33.94 (C_2), 30.95 (C_{12}), 26.90 (C_{20}), 26.31 (C_6), 26.15 (C_{16}), 25.59 (C_{11}), 23.52 (C_{26}), 21.30 ($C_{23,}$ C_{24}), 16.14 (C_{27}), 15.93 (C_{28}), 14.79 (C_{25}), 12.83 (C_{29}); ESI-HRMS Calcd for $C_{36}H_{52}O_3N^{79}BrNa$ $[M+Na]^+$ 648.3026, found 648.3022; Isotopic peak Calcd for $C_{36}H_{52}O_3N^{81}Br$ $[M+Na]^+$ 650.3008.

*4.1.8. General procedure for the synthesis of compounds (**10a-10d**)*

To a solution of compound **8** (60 mg, 0.12 mmol) in dry acetone (2 mL) anhydrous potassium carbonate (25 mg, 0.18 mmol) was added and stirred at room temperature for 30 min, then alkyl iodide (0.3 mmol) was added and continued stirring for another 2 h. After completion of the reaction, solvent was removed and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography with *n*-hexane:ethyl acetate (98:2 to 90:10 v/v) to afford the desired pure products in 66–85% yield.

*4.1.8.1. (5S,8R,9R,10S)-methyl-3-oxo-8-hydroxypolypoda-13E,17E,21E-30-trienoate (**10a**)*. Yield 81%; light yellow semi solid; R_f = 0.50 (25% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3509, 2937, 2862, 1709, 1649, 1444, 1384, 1271, 1124, 1082, 927, 747, 590; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-26), 1.30–1.56 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.59 (s, 6H, CH_3-27, CH_3-28), 1.82 (s, 3H, CH_3-29), 1.87–2.16 (m, 12H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.26 (m, 2H, CH_2-20), 2.38 (m, 1H, CH-2), 2.58 (m, 1H, CH-2), 3.72 (s, 3H, $-OCH_3$), 5.14 (m, 2H, CH-13, CH-17), 6.73 (t, 1H, J = 7.32 Hz, CH-21). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.80 (C_3), 168.52 (C_{30}), 142.21 (C_{21}), 135.04 (C_{18}), 133.67 (C_{14}), 127.23 (C_{22}), 124.88 (C_{13}), 124.67 (C_{17}), 73.40 (C_8), 60.17 (C_9), 54.96 (C_5), 51.55 ($-OCH_3$), 47.34 (C_4), 43.55 (C_7), 39.39 (C_{19}), 38.40 (C_{10}), 38.14 (C_1), 38.04 (C_{15}), 33.80 (C_2), 31.06 (C_{12}), 27.11 (C_{20}), 26.40 (C_6), 26.10 (C_{16}), 25.61 (C_{11}), 23.43 (C_{26}), 21.19 ($C_{23,}$ C_{24}), 16.06 (C_{27}), 15.84 (C_{28}), 14.68 (C_{25}), 12.27 (C_{29}); ESI-HRMS Calcd for $C_{31}H_{50}O_4$ $[M+Na]^+$ 509.3610, found 509.3601.

*4.1.8.2. (5S,8R,9R,10S)-ethyl-3-oxo-8-hydroxypolypoda-13E,17E,21E-30-trienoate (**10b**)*. Yield 85%; light yellow semi solid; R_f = 0.58 (20% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3504, 2927, 2857, 1706, 1649, 1454, 1383, 1269, 1181, 1123, 1081, 925, 748, 588; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3-25), 1.00 (s, 3H, CH_3-24), 1.08 (s, 3H, CH_3-23), 1.17 (s, 3H, CH_3-26), 1.27 (t, 3H, J = 7.17 Hz, $-CH_3$), 1.33–1.50 (m, 6H, CH-9, CH_2-11, CH_2-6, CH-5), 1.59 (s, 6H, CH_3-27, CH_3-28), 1.81 (s, 3H, CH_3-29), 1.86–2.16 (m, 12H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.25 (m, 2H, CH_2-20), 2.38 (m, 1H, CH-2), 2.57 (m, 1H, CH-2), 4.17 (q, 2H, J = 7.01 Hz, $-OCH_2-$), 5.14 (m, 2H, CH-13, CH-17), 6.72 (t, 1H, J = 7.32 Hz, CH-21). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.82 (C_3), 168.14 (C_{30}), 141.88 (C_{21}), 135.26 (C_{18}), 133.87 (C_{14}), 127.64 (C_{22}), 124.95 (C_{13}), 124.72 (C_{17}), 73.55 (C_8), 60.32 ($-OCH_2-$), 60.28 (C_9), 55.09 (C_5), 47.43 (C_4), 43.71 (C_7), 39.51 (C_{19}), 38.52 (C_{10}), 38.25 (C_1), 38.17 (C_{15}), 33.90 (C_2), 31.12 (C_{12}), 27.25 (C_{20}), 26.53 (C_6), 26.23 (C_{16}), 25.69 (C_{11}), 23.56 (C_{26}), 21.28 ($C_{23,}$ C_{24}), 16.16 (C_{27}), 15.92 (C_{28}), 14.76 (C_{25}), 14.24 ($-CH_3$),12.32 (C_{29}); ESI-HRMS Calcd for $C_{32}H_{52}O_4$ $[M+Na]^+$ 523.3746, found 523.3757.

*4.1.8.3. (5S,8R,9R,10S)-propyl-3-oxo-8-hydroxypolypoda-13E,17E,21E-30-trienoate (**10c**)*. Yield 79%; light yellow semi solid; R_f = 0.61 (20% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3482, 2928, 2858, 1706, 1648, 1456, 1385, 1268, 1123, 1080, 927, 764, 590; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H, CH_3-25), 0.95 (t, 3H, J = 3.70 Hz, $-CH_3$), 1.02 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.19 (s, 3H, CH_3-26), 1.44–1.54 (m, 8H, CH-9, CH_2-11, CH_2-6, CH-5, CH_2-7), 1.59 (s, 6H, CH_3-27, CH_3-28), 1.67 (m, 2H, $-CH_2-$), 1.83 (s, 3H, CH_3-29), 1.89–2.15 (m, 10H, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.27 (m, 2H, CH_2-20), 2.40 (m, 1H, CH-2), 2.60 (m, 1H, CH-2), 4.08 (t, 2H, J = 6.79 Hz, $-OCH_2-$), 5.16 (m, 2H, CH-13, CH-17), 6.74 (t, 1H, J = 7.55 Hz, CH-21). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.79 (C_3), 168.26 (C_{30}), 141.86 (C_{21}), 135.27 (C_{18}), 133.88 (C_{14}), 127.69 (C_{22}), 125.00 (C_{13}), 124.73 (C_{17}), 73.57 (C_8), 66.00 ($-OCH_2-$), 60.30 (C_9), 55.12 (C_5), 47.44 (C_4), 43.74 (C_7), 39.53 (C_{19}), 38.54 (C_{10}), 38.27 (C_1), 38.20 (C_{15}), 33.90 (C_2), 31.13 (C_{12}), 27.25 (C_{20}), 26.56 (C_6), 26.26 (C_{16}), 25.70 (C_{11}), 23.58 (C_{26}), 22.02 ($-CH_2-$), 21.30 ($C_{23,}$ C_{24}), 16.16 (C_{27}), 15.93 (C_{28}), 14.78 (C_{25}), 12.33 (C_{29}), 10.06 ($-CH_3$); ESI-HRMS Calcd for $C_{33}H_{54}O_4$ $[M+Na]^+$ 537.3901, found 537.3914.

*4.1.8.4. (5S,8R,9R,10S)-butyl-3-oxo-8-hydroxypolypoda-13E,17E,21E-30-trienoate (**10d**).* Yield 66%; light yellow semi solid; R_f = 0.65 (20% *n*-hexane:ethyl acetate); IR (KBr, cm^{-1}): 3500, 2930, 2862, 1705, 1647, 1457, 1384, 1270, 1124, 1080, 928, 757, 590; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, 3H, J = 7.45 Hz, $-CH_3$), 0.94 (s, 3H, CH_3-25), 1.01 (s, 3H, CH_3-24), 1.09 (s, 3H, CH_3-23), 1.19 (s, 3H, CH_3-26), 1.40–1.53 (m, 8H, CH-9, CH_2-11, CH_2-6, CH-5, $-CH_2-$), 1.60 (s, 6H, CH_3-27, CH_3-28), 1.64 (m, 2H, $-CH_2-$), 1.82 (s, 3H, CH_3-29), 1.87–2.16 (m, 12H, CH_2-7, CH_2-1, CH_2-19, CH_2-12, CH_2-15, CH_2-16), 2.26 (m, 2H, CH_2-20), 2.39 (m, 1H, CH-2), 2.59 (m, 1H, CH-2), 4.12 (t, 2H, J = 6.60 Hz, $-OCH_2-$), 5.14 (m, 2H, CH-13, CH-17), 6.72 (t, 1H, J = 7.21 Hz, CH-21). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.84 (C_3), 168.28 (C_{30}), 141.87 (C_{21}), 135.30 (C_{18}), 133.90 (C_{14}), 127.68 (C_{22}), 125.00 (C_{13}), 124.72 (C_{17}), 73.59 (C_8), 64.27 ($-OCH_2-$), 60.31 (C_9), 55.11 (C_5), 47.45 (C_4), 43.74 (C_7), 39.54 (C_{19}), 38.55 (C_{10}), 38.26 (C_1), 38.20 (C_{15}), 33.92 (C_2), 31.13 (C_{12}), 30.72 ($-CH_2-$), 27.25 (C_{20}), 26.56 (C_6), 26.25 (C_{16}), 25.71 (C_{11}), 23.58 (C_{26}), 21.30 ($C_{23,}$ C_{24}), 19.22 ($-CH_2-CH_3$), 16.17 (C_{27}), 15.93 (C_{28}), 14.80 (C_{25}), 13.73 ($-CH_3$), 12.35 (C_{29}); ESI-HRMS Calcd for $C_{34}H_{56}O_4$ $[M+Na]^+$ 551.4059, found 551.4070.

4.2. Biology

4.2.1. Cell cycle analysis

Flow cytometric analysis (FACS) was performed to calculate the population cells in different phases of cell cycle analysis. Cells (MCF-7, HT-29 and DU145) were incubated with compounds **4b, 9d and 9i** at 2.5 µM, 5 µM and 10 µM concentrations in six-well plates (1×10^5 cells/mL) for 24 h. After treatment, cells were collected, washed with PBS buffer and fixed overnight in ice-cold 70% ethanol and stained with propidium iodide. Fixed cells were pelleted and stained with buffer reagent for 30 min at 37 °C and about 10,000 events were analyzed by using flow cytometer (BD FACSVerse™, USA).

4.2.2. Phase contrast microscopy

Cells (MCF-7, HT-29 and DU145) were seeded in 96-well plate at a density of 1×10^5 cells/ mL to grow for 24 h. After incubation, cells were treated with varied concentrations of compounds **4b**, **9d** and **9i** for 48 h and images was visualized under magnification of 200× microscope (Nikon 80i, Japan).

4.2.3. Acridine orange/ethidium bromide (AO/EB) staining

Cells (MCF-7, HT-29 and DU145) were plated at a density of 1×10^6 cell/ mL and treated with different concentration of compounds **4b**, **9d** and **9i**. Plates were incubated at atmosphere of 5% CO_2 at 37 °C for 48 h, after incubation Acridine Orange (AO) and Ethidium Bromide (EB) fluorescent dyes was added to each well in equal volumes (10 µg/mL) respectively. Further, cells were visualized by fluorescence microscope (Nikon, Inc. Japan) at 200× magnification.

4.2.4. DAPI staining

Cells (MCF-7, HT-29 and DU145) were exposed to compounds **4b**, **9d** and **9i** with varied concentrations (2.5 µM, 5 µM, 10 µM) for 48 h in 96-well plate at a density of 1×10^5 cells/ mL. After incubation, cells were washed with PBS then permeabilized with fixing solution (1% formalin in PBS) for 10 min followed by staining with DAPI at concentration of 10 µM. After, control and treated cells were visualized under fluorescence microscope (Nikon, Japan) at 200× magnification.

*4.2.5. **Mitochondrial membrane potential** (ΔΨm)*

Cells (MCF-7, HT-29 and DU145) were seeded in 6 well plates at density 1×10^6 cells/ mL and allowed to adhere for overnight. The cells were treated with 2.5 µM, 5 µM and 10 µM concentrations of respective compounds **4b**, **9d** and **9i** for 24 h. After incubation cells were collected, washed with PBS and resuspended in solution of JC-1 (10 µg/mL) for 10 min at 37 °C. Further, cells were analyzed under fluorescence microscope (Nikon, Japan) at 200× magnification.

4.2.6. Reactive oxygen species (ROS)

Cells (MCF-7, HT-29 and DU145) were plated at density of 1×10^6 cells/mL in 6 well culture plates and allowed to grow for overnight. These cells were treated with 2.5 µM, 5 µM and 10 µM concentrations of the compounds **4b, 9d** and **9i** for 24 h. After incubation, medium was removed; cells were washed with PBS and treated with 4% formalin solution. Further, cells were exposed with DCFDA dye in 10 µM concentration and incubated at room temperature in dark for 30 min. The intensity of fluorescence was increased because of generation of reactive oxygen species was analyzed by spectrofluorometer.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2018.10.039.

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