# Natural Sesquiterpenoids as Cytotoxic Anticancer Agents

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**Abstract:** Sesquiterpenoids are a group of naturally occurring 15-carbon isoprenoid compounds that are mainly found in higher plants, microorganism and marine life. Many of them provided encouraging leads for chemotherapeutics. In this review, the sesquiterpenoids are classified according to the ring numbering system and the functional groups presented in the core structures as acyclic, mono-, bi-, and tricyclic derivatives, and a current overview of sesquiterpenoids as potential cytotoxic anticancer agents is provided.

**Keywords:** Anticancer, cancer, cytotoxicity, natural products, sesquiterpenoids, tumor.

## 1. INTRODUCTION

Cancer is the uncontrolled growth of cells coupled with malignant behavior: invasion and metastasis. Cancer is thought to be caused by the interaction between genetic susceptibility and environmental toxins. In the broad sense, most chemotherapeutic drugs cause damage to cells, such as through impairing the mitosis (cell division), effectively targeting fast-dividing cell, so these drugs are termed cytotoxic. In general, cytotoxic anticancer agents are classified as alkylating agents, platinums, anti-metabolites, anti-mitotics, topoisomerase I inhibitors, topoisomerase II inhibitors, DNA intercalators, and DNA cleaving agents. In spite of the large number of chemotherapeutic agents available in clinic, the medical need is still largely unmet. The main reasons include: (1) the lack of selectivity of conventional drugs, leading to toxicity; (2) the metastatic spreading, implying early tumor implantation in organs other than primary site; (3) the heterogeneity of the disease, comprising about 100 types of cancer; (4) the intrinsic or acquired resistance to chemotherapy developed after few therapeutic cycles, i.e. multi-drug resistance [1]. It is thus no surprise that cancer is a major cause of deaths worldwide.

The last century witnessed dramatic advances in cancer therapeutics. A number of innovative strategies are in development, aimed at targeting the malignant abnormalities of tumor cells arising from the activation of tumor promoter genes or inhibition of tumor suppressor genes. Such therapies are expected to target specifically tumor cells, thus allowing for strong anticancer effects and minimal toxicities. Advances in molecular biology have identified numerous steps and proteins involved in malignant transformation as targets of anticancer therapy, such as oncogene encoded proteins acting as signal transducer like Ras, mainly targeted at the prenylation step by farnesyl transferase inhibitors [2], cell cycle targets as cyclin-dependent kinases [3], telomerase [4], histone deacetylases [5], epidermal growth factor receptor (EGFR) tyrosine kinases [6], among many others. A number of such target-based anticancer therapies are now successfully used in routine clinical practice [7]. For example, in chronic myelogenous leukemia, the Abelson tyrosine kinase inhibitor Imatinib (Gleevec) targets the activity of BCR-ABL oncoprotein; in acute promyelocytic leukemia (APL), all-trans-retinoic acid (ATRA) or arsenic trioxide ($As_2O_3$) targets PML-RARα fusion. The introduction of ATRA or Imatinib in the treatment of APL or chronic myelogenous leukemia patients has significantly improved the management of these diseases.

In spite of these successes, the development of molecular-target-based drugs faces some difficulties. On one hand, the molecular selectivity itself may require an increased use of tumor genotyping to guide the choice of the drugs, which may anyway face the problem of tumors genetic instability [8]. On the other hand, most molecular-target-based drugs may have cytostatic rather than cytotoxic effects, the traditional clinical strategies for the evaluation of chemotherapeutic drugs which are based on tumor shrinkage at the maximum-tolerated dose may not be appropriate [9]. This is the case that several molecular-targeted MMP inhibitors (MMPI) failed in phase III trials, in spite of the strong biological rationale and the many evidences of efficacy in mouse models [10]. In fact, cytotoxic anticancer drugs like taxanes and camptothecins (CPTs) still represent milestones in cancer treatment. It is believed that cytotoxic drugs will continue to represent a chief part of the therapy in the near future, also in combination with the molecular-target-based drugs and this may imply a need for new drugs with better activity and safety profile. Moreover, the traditional cytotoxic approaches received in the recent past and will still receive in the near future useful support by new available mechanistic information, both in terms of screening

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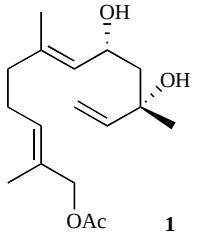
1389-5575/11 $58.00+.00 

of new agents and rational drug design of synthetic or semi-synthetic second generation analogs [1].

Natural products are important sources in drug discoveries and developments. In the area of cancer, over the time frame from around the 1940s to 2007, of the 155 small molecules, 47% are either natural products or directly derived therefrom [11]. Sesquiterpenoids are a group of 15-carbon compounds derived from the assembly of 3 isoprenoid units. Found mainly in higher plants and microorganism, many of them have biological activity, including antimicrobial, antitumor, and cytotoxic properties. In plants, they play important ecological roles in interactions with insects and microbes and act as attractants, deterrents, antifeedants and phytoalexins [12, 13]. In this review, sesquiterpenoids are classified according to their ring numbering system and the functional groups presented in their structures as acyclic, monocyclic, bicyclic and tricyclic derivatives, and their roles as cytotoxic anticancer agents are introduced. The authors attempt to provide a highly subjective selection of results published in the scientific literature mostly from the year of 2000 to 2010 using SciFinder® as a general searching tool.

## 2. ACYCLIC SESQUITERPENOIDS

There are few natural acyclic sesquiterpenoids with reported cytotoxic activities. Kinghorn's group isolated a nerolidol derivative (Fig. (**1**)) from the flowers and leaves of *Ratibida columnifera* [14]. It was evaluated for cytotoxicity in a 25 cell line tumor panel, representing a diverse group of mouse and human tumors, fibroblasts, and normal bovine endothelial cells. The nerolidol **1** showed generally weak cytotoxic activities, with $ED_{50}$ values of 8.7, 9.5, 3.5 and 10.9 μg/mL towards human breast cancer (BCl), human fibrosarcoma (HT), human epidermoid carcinoma (KB) and multidrug-resistant KB cells, respectively.



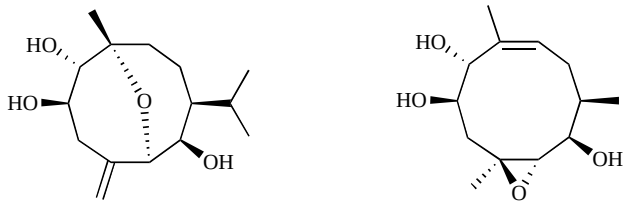

**1**

**Fig. (1).** Nerolidol derivative **1**.

## 3. MONOCYCLIC SESQUITERPENOIDS

### 3.1. Sesquiterpenoid Alcohols

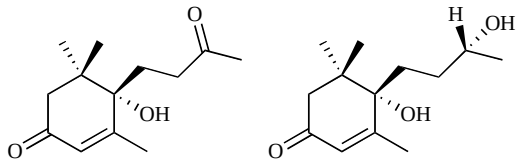
Giovanni's group isolated 11 germacrane sesquiterpenoids from the aerial part of *Santolina insularis* [15]. The isolated germacrane sesquiterpenes were evaluated for cytotoxic activity against Caco-2 (human colon carcinoma) and peritoneal macrophages cell lines. While all the tested compounds were inactive against the second cell line ($IC_{50}$ >10 μg/mL), two new sesquiterpenoid alcohols **2** and **3** (Fig. (**2**)) exhibited potent cytotoxic activity against the human colon carcinoma cell line, with $IC_{50}$ of 1.0 μg/mL (3.7 μM) and 0.3 μg/mL (1.1 μM), respectively. Furthermore, the close similarity between the active compounds and the inactive compounds suggests that subtle structural changes can dramatically influence the cytotoxic activity within this class of compounds.




**2** **3**

**Fig. (2).** Germacrane sesquiterpenoid alcohols.

Two known sesquiterpenoid alcohols, dehydrovomifoliol (**4**) and blumenol A (**5**), were isolated from the whole plant of *Solanum lyratum* [16]. They were evaluated for their cytotoxic activities against HONE-1 nasopharyngeal, KB oral epidermoid carcinoma, and HT29 colorectal carcinoma cell lines using anticancer drugs etoposide and cisplatin as positive controls. Dehydrovomifoliol (**4**) and blumenol A (**5**) exhibited significant cytotoxicity with $IC_{50}$ values in the range of 3.9~6.0 μM, comparable with that of cisplatin (Fig. (**3**)).




**4** **5**

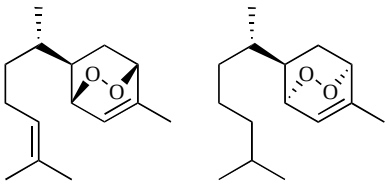
$IC_{50}$ (μM)

| | HONE-1 | KB | HT29 |
|---|---|---|---|
| **4** | 4.8±1.2 | 4.0±1.9 | 5.7±2.1 |
| **5** | 4.3±1.5 | 3.9±2.0 | 6.0±3.1 |
| etoposide | 0.6±0.4 | 0.9±0.3 | 1.9±0.6 |
| cisplatin | 3.8±0.4 | 4.5±0.7 | 5.8±1.2 |

**Fig. (3).** Dehydrovomifoliol and blumenol A and cytotoxic activities.

### 3.2. Sesquiterpenoid Endoperoxides

Terpene peroxides are very interesting topics because they frequently possess many biological activities such as cytotoxic and antiviral activities. Two sesquiterpenoid endoperoxides, (1*S*,4*R*,6*R*)-1,4-endoperoxy-bisabola-2,10-diene (**6**) and (1*R*,4*S*,6*R*)-1,4-endoperocy-bisabola-2,10-diene (**7**), were isolated from the aerial parts of *Artemisia stolonifera* (Compositae) [17]. The *in vitro* cytotoxicity of compounds **6** and **7** against cultured human tumor cell lines, A549 (non small cell lung adenocarcinoma), SK-OV-3 (ovarian), SK-MEL-2 (skin melanoma), XF498 (CNS) and HCT15 (colon), was studied, and the results are shown in Fig. (**4**), using anticancer drug doxorubicin as a positive control. They exhibited potent cytotoxicity against five



**6** **7**

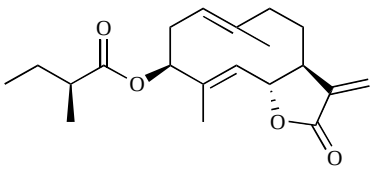
| | $ED_{50}$ (μg/mL) | | | | |
|---|---|---|---|---|---|
| | A549 | SK-OV-3 | SK-MEL-2 | XF498 | HCT15 |
| **6** | 5.43 | 0.24 | 1.20 | 2.65 | 0.29 |
| **7** | 0.87 | <0.1 | 0.19 | 0.32 | 0.14 |
| doxorubicin | 0.12 | 0.13 | 0.11 | 0.23 | 2.40 |

**Fig. (4).** Sesquiterpenoid endoperoxides and cytotoxic activities.

human tumor cell lines with their $ED_{50}$ values ranging from 0.29 to 5.43 μg/mL and from <0.1 to 0.87 μg/mL, respectively. Compound **7** showed extremely strong cytotoxic activity against SK-OV-3 with an $ED_{50}$ value of < 0.1 μg/mL.

### 3.3. Sesquiterpenoid Lactones

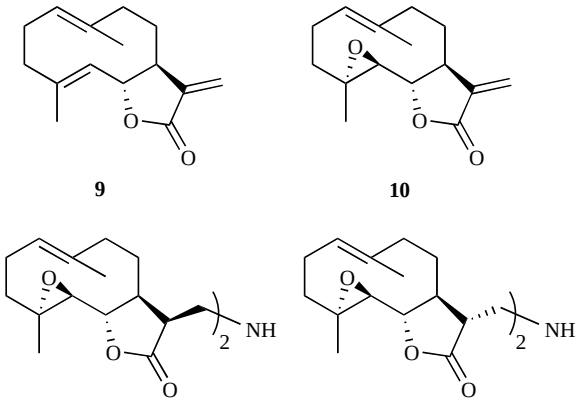
Sesquiterpenoid lactone **8** (Fig. (**5**)) was obtained as a yellowish, amorphous powder from the aerial parts of *Artemisia princeps* PAMPANINI (Sajabalssuk) through repeated silica gel and octadecyl silica gel (ODS) column chromatography [18]. In the MTT cytotoxicity assay, compound **8** exhibited high potent activity almost identical to the well known anticancer drug, cisplatin. The $IC_{50}$ values of **8** against human cervical adenocarcinoma (HeLa), human leukemia (U937) and human lung adenocarcinoma (A549) cell lines were 15.5, 16.0 and 22.1 μg/mL, respectively. Because apoptosis-inducing compounds are potential antitumor agents, lactone **8** was tested to induce apoptosis in HeLa cells. Compared to the control cells (0.64%), treatment with compound **8** (15 μg/mL) for 24 h resulted in 41.44% sub-G1 ratio. In addition, compound **8** also induced DNA fragmentation in a concentration-dependent manner in the HeLa cells. As the cytosolic aspartate-specific proteases, called caspases, are suggested to be responsible for the intentional disassembly of a cell into apoptotic bodies, the involvement of caspase activation in compound **8**-induced apoptosis in HeLa cells was examined by Western blotting assay. Treatment of cells with lactone **8** at the concentration of 2.5 and 10 μg/mL for 24 h increased the cleavage form of procaspase-3. These results indicate that compound **8** is a potent inducer of apoptosis in HeLa cells *via* caspase-3 activation.



**8**

**Fig. (5).** Sesquiterpenoid lactone **8**.

Four germacrane-type sesquiterpenoid lactones costunolide (**9**), parthenolide (**10**), isobisparthenolidine (**11**) and bisparthenolidine (**12**) were isolated from the chloroform-soluble fraction of the methanolic extract of the bark of *Magnolia kobus* (Magnoliaceae) through repeated silica gel and Sephadex LH-20 column chromatography [19]. The cytotoxic activities of the isolated compounds were evaluated against four cultured human tumor cells, A549, SK-OV-3, SKMEL-2 and HCT15 (Fig. (**6**)). Among them, parthenolide (**10**) exhibited the most potent cytotoxicity against the four tumor cell lines with $ED_{50}$ in the range of 1.3 to 3.1 μg/mL, while costunolide (**9**) and bisparthenolidine (**12**) showed moderate cytotoxicities. Isobisparthenolidine (**11**) is an isomer of bisparthenolidine (**12**), but it showed more potent cytoxicities than **12**.



**9** **10**

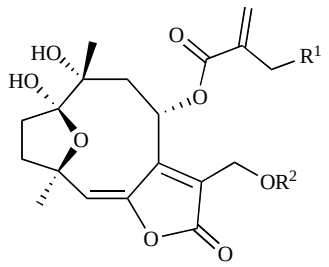
**11** **12**

| | $ED_{50}$ (μg/mL) | | | |
|---|---|---|---|---|
| | A549 | SK-OV-3 | SK-MEL-2 | HCT15 |
| **9** | 14.4 | 9.9 | 8.7 | 13.7 |
| **10** | 3.1 | 2.4 | 1.3 | 1.6 |
| **11** | 2.0 | 1.9 | 3.9 | 3.2 |
| **12** | 11.4 | 9.1 | 6.2 | 7.6 |
| doxorubicin | 0.01 | 0.13 | 0.01 | 0.1 |

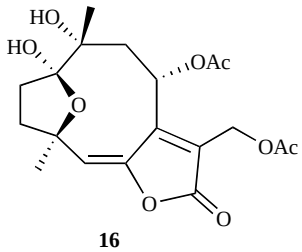
**Fig. (6).** Costunolide, parthenolide, isobisparthenolidine and bisparthenolidine.

Yue's group reported the isolation of 4 sesquiterpenoid lactones from the aerial part of Vernonia bockiana [20]. The cytotoxicities of isolated compounds were tested against P388 (mouse lymphoid tumor) and A549 (human lung cancer) cell lines. Vernobockolide B (**13**), piptocarphin F (**14**), piptocarphin A (**15**) and hirsutolide (**16**) showed significant activity against P388 with the $IC_{50}$ values of 1.81, 1.32, 0.77 and 0.73 μM, respectively, while all compounds were inactive against A549 tumor cell line (Fig. (**7**)).

*Achillea* species have been widely applied in folk medicine for the treatment of different cancers, tumors and



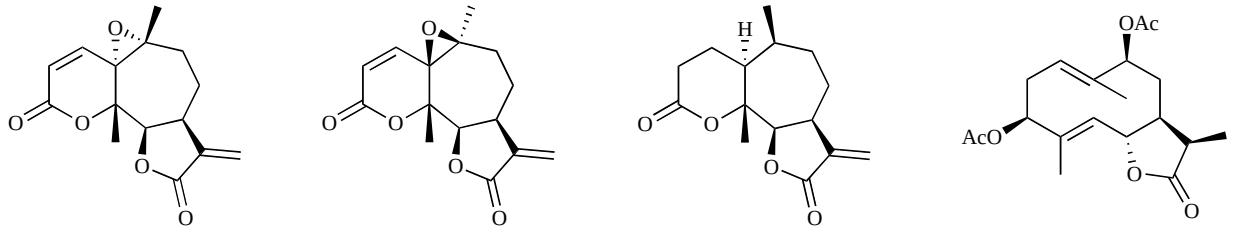
| | $R^1$ | $R^2$ |
|---|---|---|
| **13** | OH | Et |
| **14** | H | Et |
| **15** | H | Ac |



**16**

**Fig. (7).** Vernobockolide B, piptocarphin F, piptocarphin A and hirsutolide.

warts. In European and American countries, yarrow has been used in the form of different preparations (juice, ointment, oil, etc.) as traditional herbal medicine against cancer of the breast and liver, and hardness of the uterus. Hohmann's group isolated 4 monocyclic sesquiterpenoids (Fig. (**8**)) from the aerial parts of the *Achillea millefolium* and studied their antiproliferative activities on three tumor cell lines (HeLa, MCF-7 and A431) [21]. The *seco*-pseudoguaianolides paulitin (**17**) and isopaulitin (**18**) exhibited potent antiproliferative effects, the $IC_{50}$ values for compound **17** were 4.76, 1.96, 1.48 μM, respectively, for the HeLa, MCF-7 and A431 cell lines, while that for compound **18** were 11.82, 13.68, 6.95 μM, respectively. Both compounds contain two α,β-unsaturated (C–O–CH=$CH_2$) systems, which might be important for the cytotoxicity of natural sesquiterpenoid lactones, as psilostachyin C (**19**), possessing only one C–O–CH=$CH_2$ moiety in the molecule, did not exhibit an antiproliferative effect. However, the presence of epoxy functionality and its stereochemistry most probably plays an important role in the antiproliferative potency, because of the significant difference in the activities of paulitin (**17**) and its epimer isopaulitin (**18**). Moreover, sintenin (**20**) which has no α,β-unsaturated (C–O–CH=$CH_2$) system was inactive towards the tested cells.



**17** **18** **19** **20**

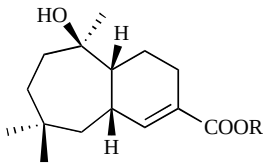
**Fig. (8).** Paulitin, isopaulitin, psilostachyin C and sintenin.

## 4. BICYCLIC SESQUITERPENOIDS

### 4.1. Sesquiterpenoid Alcohols

Malfilanol A (**21**) and malfilanol B (**22**) (Fig. (**9**)) were two sesquiterpenoid alcohols isolated from the fungus *Malbranchea filamentosa* IFM41300 [22]. They were tested for cytotoxic activities against human umbilical vein endothelial cells (HUVEC) and A549 human lung cancer cells. Malfilanol A and B inhibited the cell proliferation of HUVEC with $IC_{50}$ values of 14.6 and 19.8 μM respectively, while malfilanol B inhibited proliferation of A549 cells with an $IC_{50}$ value of 7.8 μM. Malfilanol A showed no inhibition of A549 cell proliferation even at the concentration of 79.4 μM.

Drimane sesquiterpenoids are widely recognized as bioactive metabolites of terrestrial plants, marine animals such as sponges and mollusks, and fungi and have attracted wide attention due to their wide biological activities, which include antibacterial, antifungal, antifeedant, plant-growth regulatory, cytotoxic, phytotoxic, piscicidal, and molluscicidal effects. Liu's group obtained drimane sesquiterpenoid alcohols **23-26** (Fig. (**10**)) from cultures of the fungus *Aspergillus ustus*, which was isolated from the marine sponge *Suberites domuncula* [23]. They were evaluated against a panel of tumor cell lines, including L5178Y, HeLa, and PC12 cells, but they were inactive at the range of concentration analyzed (0.1-10 μg/mL). Zhu's group isolated sesquiterpenoid alcohols **26-29** (Fig. (**10**)) from the EtOAc extract of the marine-derived fungus *Aspergillus ustus* 094102 [24]. Only ustusolate A (**29**) showed weak cytotoxicity against HL-60 and A549 cell lines with an $IC_{50}$ value of 20.6 and 30.0 μM, respectively.



**21:** Malfilanol A; R = H.

**22:** Malfilanol B; R = $CH_3$.

**Fig. (9).** Malfilanol A and B.

### 4.2. Sesquiterpenoid Lactones

Carlaolides A (**30**) and B (**31**) (Fig. (**11**)) were isolated from the aerial parts of *Artemisia princeps* PAMPANINI (Sajabalssuk) [18]. Carlaolides A and B exhibited significant

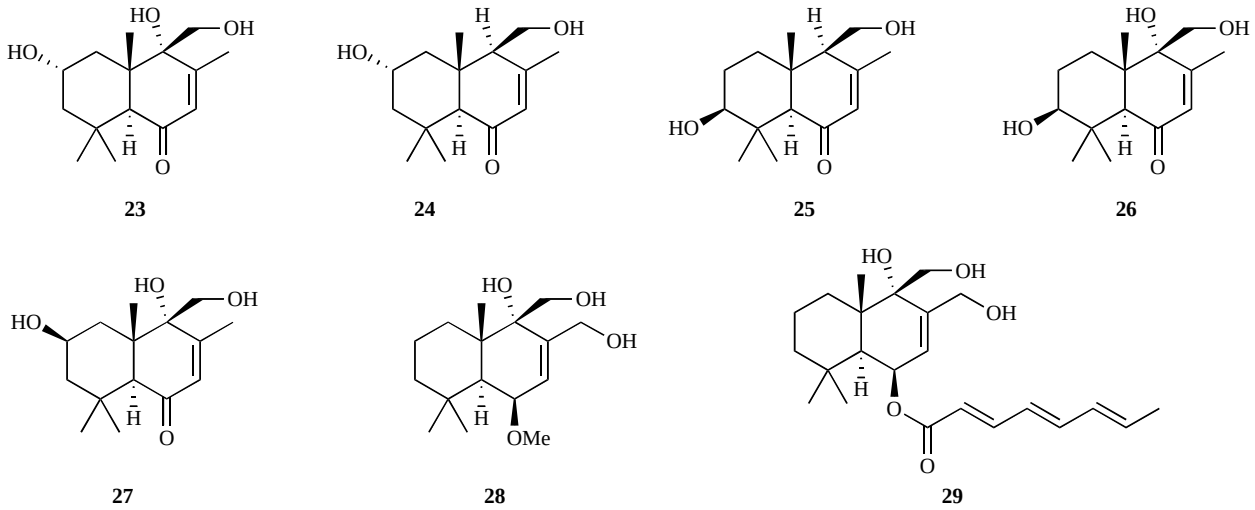



**Fig. (10).** Sesquiterpenoid alcohols **23-29**.

activities against human cervical adenocarcinoma (HeLa), human leukemia (U937) and human lung adenocarcinoma (A549) cell lines. The $IC_{50}$ values of carlaolide A were 22.9, 22.6 and 40.5 μg/mL, respectively, for HeLa, U937 and A549 cell lines, while that for carlaolide B were 22.8, 17.2 and 43.5 μg/mL, respectively.

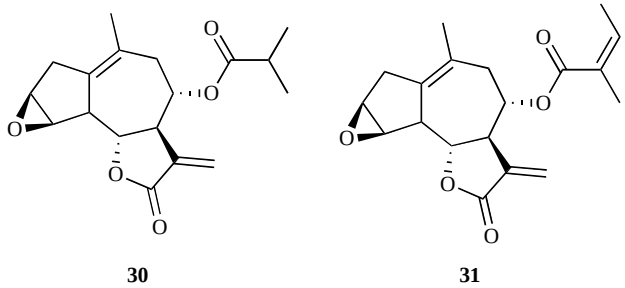



**Fig. (11).** Carlaolide A and B.

Drimane sesquiterpene lactones **32-40** (Fig. (**12**)) were also found in the marine-derived fungus *Aspergillus ustus* [23, 24]. Liu's group evaluated the cytotoxicities of sesquiterpene lactones **32-37** against a panel of tumor cell lines, including L5178Y, PC12 and HeLa cells [23]. Compound **33** was only active against L5178Y cells with an $EC_{50}$ value of 5.3 μg/mL. Compound **36** was the most active, and its $EC_{50}$ values were 0.6, 7.2, 5.9 μg/mL, respectively, for the L5178Y, PC12 and HeLa cells. Lactone **37** was active against L5178Y and HeLa cells with the $EC_{50}$ values of 1.9 and 7.5 μg/mL, respectively. All other compounds were inactive at the concentrations of 0.1 to 10 μg/mL. All cytotoxic compounds featured an olefinic ester side chain comprising two (**33** and **36**) or three conjugated olefinic double bonds (**37**) with a terminal carboxylic, aldehyde, or methyl substituent. Absence of the ester side chain as observed for **32** resulted in a loss of cytotoxic activity. Though the isomeric compounds **34** and **35** also feature an olefinic ester side chain, they are inactive compared to **33**, **36**, and **37**. It seemed that the two vicinal OH functions in the side chain of **34/35** might nullify the bioactivity. When tested against PC12 or HeLa cells, compounds **33**, **36** and **37** were far less active than observed for the lymphoma cell line L5178Y. The $EC_{50}$ value of the most active congener (**36**) dropped 10-fold from 0.6 μg/mL to 5.9 μg/mL against HeLa cells, whereas the $EC_{50}$ value against PC12 cells was 7.2 μg/mL. Similar trends were observed for **33** and **37**, suggesting a cell line specificity.

Zhu's group investigated the cytotoxic effects of compounds **36-40** on A549 and HL-60 cell lines. Ustusolates **36** and **39** exhibited moderate cytotoxicity against HL-60

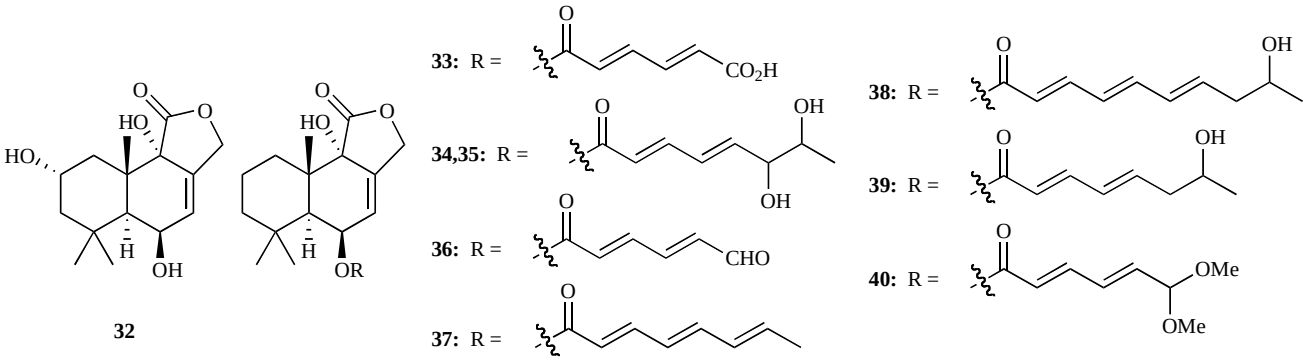



**Fig. (12).** Drimane sesquiterpene lactones.

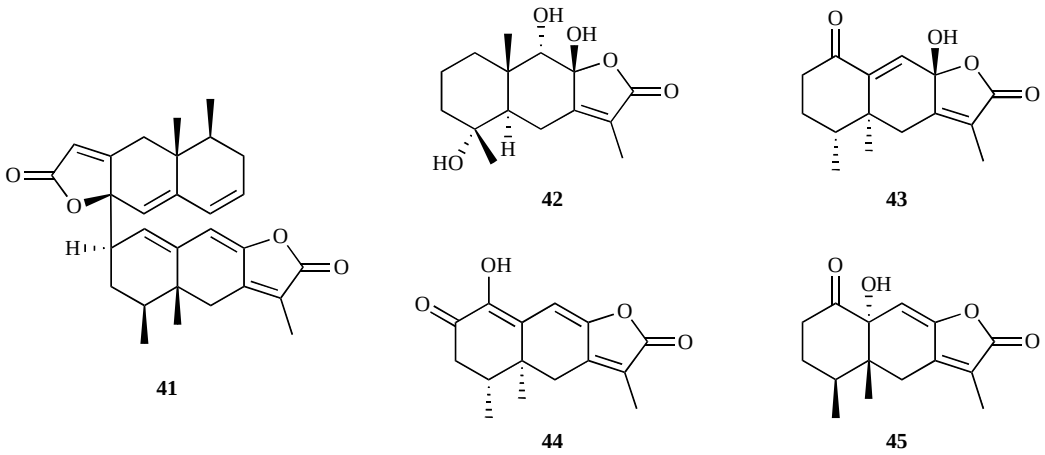



**Fig. (13).** Sesquiterpenoid lactones **41-45**.

and A549 cells with an $IC_{50}$ value of 9.0 and 10.5 μM, respectively [24]. The other compounds were inactive to both human cancer cell lines ($IC_{50}$ >100 μM).

The genus *Ligularia* (Asteraceae) contains more than 110 species distributed in China, of which about 40 species have been used as traditional Chinese medicine or folk herbs with antibiotic, antiphlogistic and antitumor activities. *Ligularia platyglossa* (Franch.) Hand.-Mazz is mainly distributed in southwest of China and local inhabitants have used its underground organs for a long time as a folk medicine to reduce phlegm and relieve cough. Wang's group isolated five sesquiterpenoid lactones **41-45** (Fig. (**13**)) from the underground organs of *Ligularia platyglossa* [25]. They were evaluated for their cytotoxicity against seven carcinoma cell lines (BGC-823, A549, HL-60, B16, SMMC-7721, BEL7402 and Hela). Compound **44** exhibited weak cytotoxic activities against B16, BEL7402, Hela carcinoma cells with $IC_{50}$ values of 167.7, 271.5 and 203.5 μM, respectively. All other compounds tested were not active towards these cells. However, compounds **43-45** exhibited medium inhibitory activities against HL-60 carcinoma cells with the $IC_{50}$ values of 24.0, 28.1 and 51.1 μM, respectively. Compound **44** induced Hela cells apoptotic death after 48 h treatment with 0.38 mM of the compound (apoptosis up to 27.04%). The comparatively wide bandwidth of cytotoxicities of **44** may possibly be due to its structural features of an enolic hydroxyl and keto groups adjacent to each other, which provide an efficient hydrogen bonding capability comparing to the other tested sesquiterpenoid lactones in this study.

### 4.3. Sesquiterpenoid Ketones

*Ulmus pumila* L. is a deciduous tree that is widely distributed in East Asia. The stem and root bark of this species have been used in traditional Chinese medicine for edema, mastitis, gastric cancer, and inflammation. Ikejima's group isolated two sesquiterpenoid ketones, mansonone E (**46**) and mansonone F (**47**) (Fig. (**14**)), from the dried root bark of *Ulmus pumila* [26]. The inhibitory effects of **47** and **48** on the proliferation of human A375-S2, HeLa, MCF-7, and U937 cells were investigated *in vitro*. The $IC_{50}$ values of **46** against the four tumor cell lines were 2.2, 7.9, 3.1, and 0.9 μM, respectively, while those of **47** were 13.3, 30.5, 29.4, and 3.0 μM, respectively. Mansonone E and F have cytotoxic activities against the four human tumor cell lines, and U937 is the most sensitive cell line to these compounds. Mansonone F (**47**) has similar antiproliferative activity compared with 5-FU, but mansonone E (**46**) was more potent. Further studies showed that **46** induced oligonucleosomal fragmentation of DNA in HeLa cells and activated caspase-3, followed by the degradation of the inhibitor of caspase-activated DNase, decreased the expression of anti-apoptotic mitochondrial proteins Bcl-2 and Bcl-$_{XL}$, and increased that of proapoptotic Bax. Thus, mansonone E (**46**) may promote tumor cell death by modulating the balance of Bcl-2 family proteins and signals to apoptotic effector molecules (caspases), which subsequently cleave key cellular proteins to generate the apoptotic morphology. But the antiproliferative activity of **46** can not be entirely blocked by caspase inhibitors, therefore other pathways might participate in inducing apoptosis in human tumor cells. The mechanism of tumor cell apoptosis induced by mansonone E remains to be further elucidated.

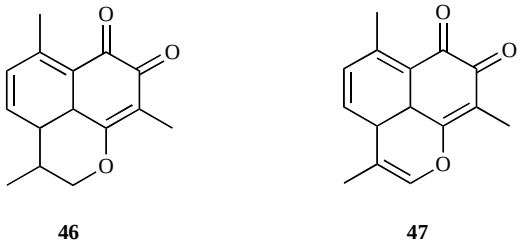
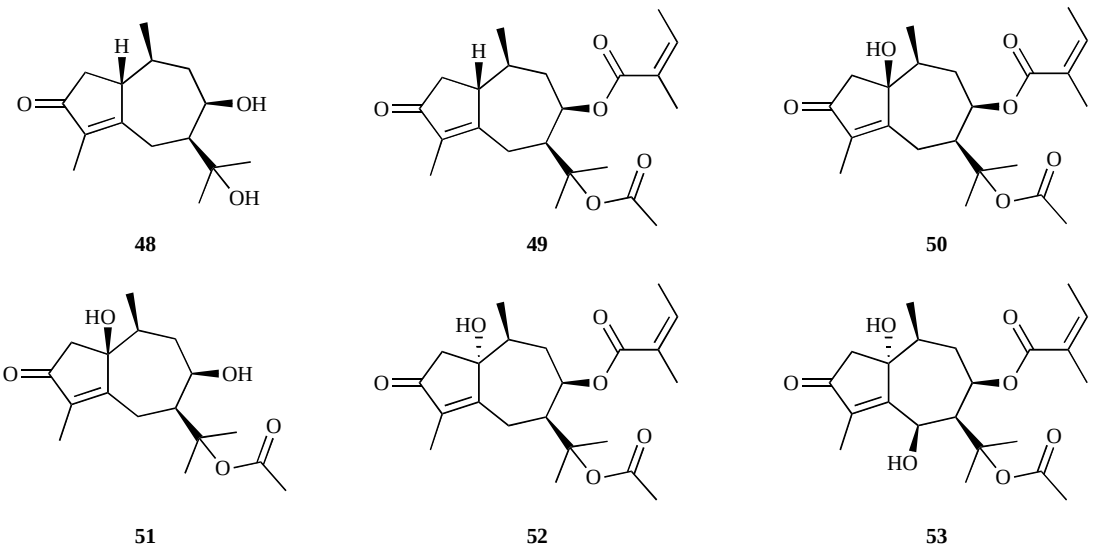



**Fig. (14).** Mansonone E and mansonone F.

The fruits of *Torilis japonica* DC. (Umbelliferae) have been used as an anti-inflammatory traditional medicine to treat skin diseases and urogenital disorders. Lee's group isolated six guaiane sesquiterpenoids **48-53** (Fig. (**15**)) from the fruits of *Torilis japonica* (Umbelliferae) [27]. These compounds were evaluated for their cytotoxic activity against the human breast cancer cells (MCF-7) and Lewis lung carcinoma (LLC) cells. Compounds **49**, **50** and **52** exhibited modest cytotoxic activity against the LLC cells with $IC_{50}$ values of 31.3, 32.5 and 34.0 μg/mL, respectively.



**48** **49** **50**

**51** **52** **53**

**Fig. (15).** Guaiane sesquiterpenoids **48-53**.

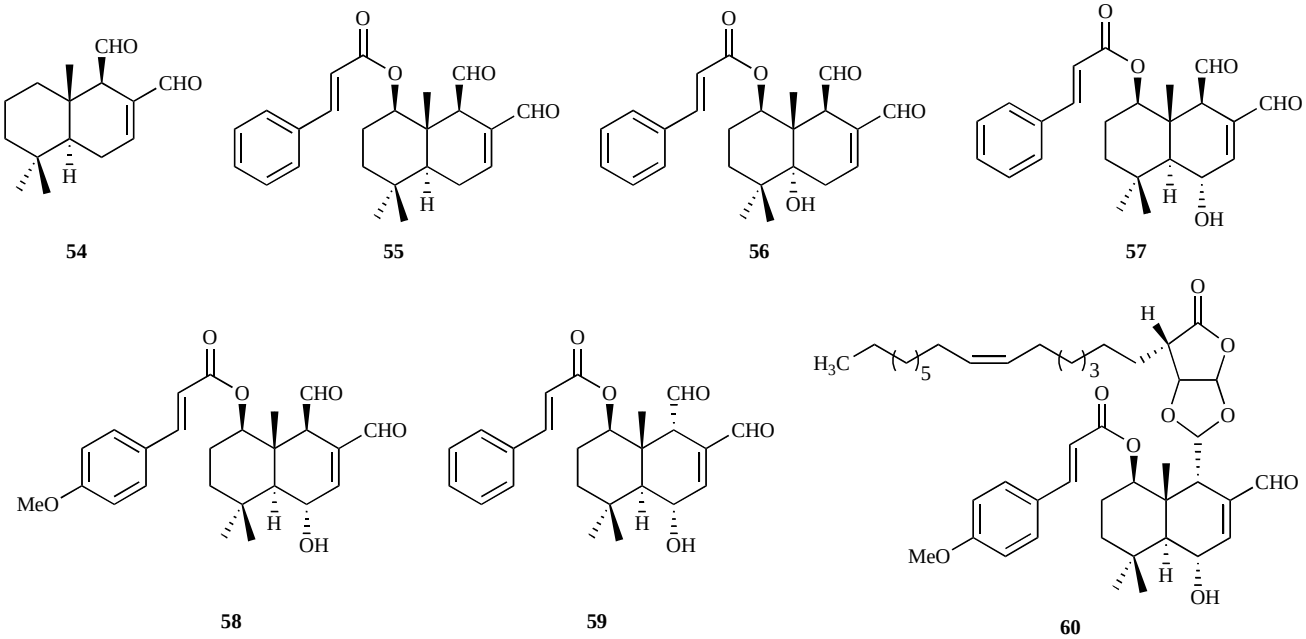
However, no significant cytotoxicity was found against the MCF-7 cells for any of the compounds tested.

### 4.4. Sesquiterpenoid Aldehydes

Seven drimane sesquiterpenoid aldehydes **54-60** (Fig. (**16**)) were isolated from the bark and leaves of *Zygogynum pancher*i and *Zygogynum acsmithii* (Winteraceae) [28]. They were subjected to a cytotoxic assay against the human KB (mouth epidermoid carcinoma), HCT116 (colon) and HL60 (promyelocytic leukemia) cancer cell lines. Compounds **54-59** exhibited significant cytotoxicities against these cancer cells, with the $IC_{50}$ values ranging from 0.1 to 1.2 μM, while compound **60** was inactive. The presence of the dialdehyde function seems to be important for a strong cytotoxicity.

### 4.5. Sesquiterpenoid Ethers

The rhizome of *Atractylodes ovata* (Bai Zhu in Chinese) is a widely used traditional Chinese herb in Taiwan as a tonic agent. Atractylon (**61**, Fig. (**17**)) was isolated from the *n*-hexane extract of the *Atractylodes ovata* and evaluated for cytotoxic effects *in vitro* [29]. Atractylon significantly inhibited the growth of human leukemia cell line HL-60 and mouse leukemia cell line P-388 at 15 μg/mL for 12 h and the inhibitory rates were 90.2 and 86.5%, respectively. It is also of notice that this compound did not induce any cytotoxicity against primary cultures of normal human peripheral blood mononuclear cells when treated at 15 μg/mL for 48 h. In accordance with DNA fragment increases and PARP protein decreases, atractylon induced apoptosis in HL-60 cells at 15

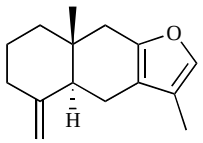


**54** **55** **56** **57**

**58** **59** **60**

**Fig. (16).** Sesquiterpenoid aldehydes **54-60**.

μg/mL for 6 h. Moreover, atractylon inhibited the viability of P388 cells and induced apoptosis after 15 μg/mL treatment for 12 h in an *in vitro* assay. These studies indicated that the growth inhibitory effects of atractylon against HL-60 cells was at least partially through the induction of programmed cell death with less cytotoxicity to normal human peripheral blood mononuclear cells.



**61**

**Fig. (17).** Atractylon.

### 4.6. Halogenated Sesquiterpenoids

Halogenated sesquiterpenoid **62**, deschloroelatol **63**, acetyldeschloroelatol **64**, elatol **65** and acetylelatol **66** (Fig. (**18**)) were isolated from the sea hare *Aplysia dactylomela* [30]. The *in vitro* cytotoxicity of the halogenated sesquiterpenoids **63-67** against two cancer cell lines (HeLa and Hep-2) and nontumoral Vero cells was evaluated by means of MTT assay. The cytotoxic activity data showed that elatol **65** was the most active compound under the two conditions (cells in lag and log-phase of growth) assayed. It is important to emphasize that when the cells are exponentially grown, the activity increases considerably in the case of elatol **65** and acetylelatol **66** against HeLa ($IC_{50}$ 1.3 and 13.7 μM, respectively) but not against Hep-2 cells. Furthermore, both compounds **65** and **66** showed selective cytotoxic activity ($IC_{50}$ 25.0 and 44.6 μM) against Vero cells. Deschloroelatol **63** and its acetyl derivative **64** were inactive ($IC_{50}$ >67 and >58 μM), which indicates the relevance of the chlorine atom in the molecule for the cell cytotoxity. The results support the hypothesis that acetyl derivatives decrease the toxicity of the corresponding alcohols and that sea hares use acetylation as a strategy to store toxic metabolites acquired through diet.

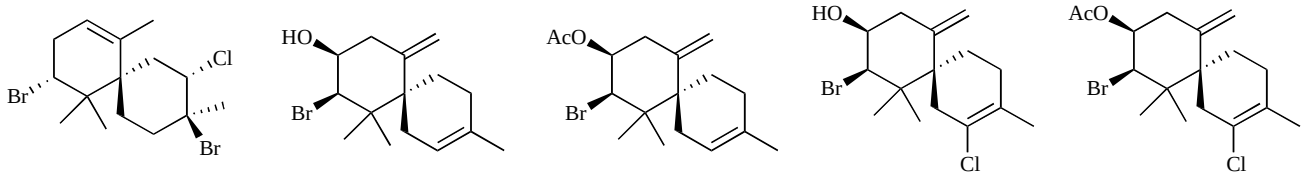
### 4.7. Sesquiterpenoid Quinones

Nakijiquinones G-I (**67-69**) (Fig. (**19**)) were isolated from Okinawan marine sponges of the family *Spongiidae* [31]. They are sesquiterpenoid quinones having an amine residue such as histamine, agmatine, and 3-(methylsulfinyl) propan-1-amino group, respectively. Nakijiquinones G-I showed modest cytotoxicity against P388 murine leukemia ($IC_{50}$: 3.2, 2.4, and 2.9 μg/mL, respectively), L1210 murine leukemia ($IC_{50}$: 2.9, 8.5, and 2.4 μg/mL, respectively), and KB human epidermoid carcinoma cells ($IC_{50}$: 4.8, >10, and 5.6 μg/mL, respectively) *in vitro*.

### 4.8. Sesquiterpenoid Glycosides

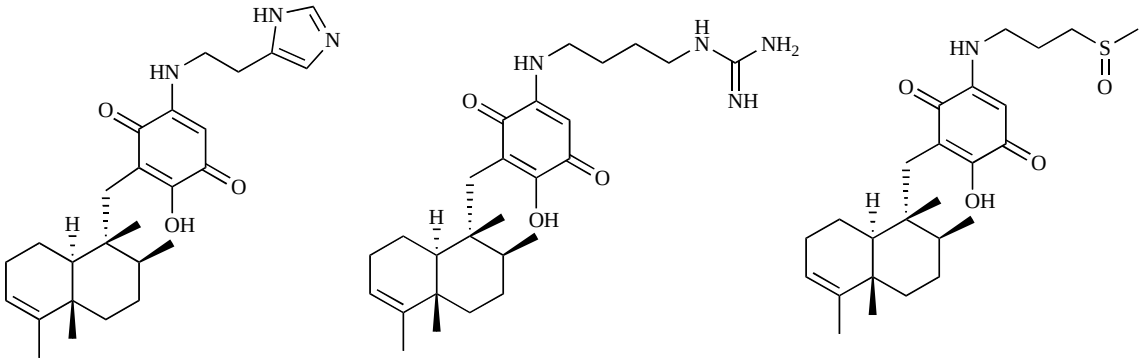
Two sulfated cadinene-type sesquiterpenoid glycosides **70** and **71** (Fig. (**20**)) were obtained from whole cottonseed (*Gossypium hirsutum*) [32]. They were screened for their toxicity on Jurkat cells (a human lymphoblastoid T cell line). Compounds **70** and **71** inhibited cellular proliferation with $IC_{50}$ values of 8.1 and 4.2 μg/mL, respectively.

Two eudesmane sesquiterpene glycosides **72** and **73** (Fig. (**21**)) were isolated from the fruits of *Cananga odorata* [33]. They were evaluated for cytotoxicity against two human hepatocarcinoma cell lines (Hep $G_2$ and Hep 2,2,15). Compound **73** was moderate cytotoxic against the Hep $G_2$ and Hep 2,2,15 cell lines, with $IC_{50}$ values of 3.9 and 10.6 μg/mL, respectively. Compound **72** displayed potent cytotoxicity against both of these cell lines ($IC_{50}$: 0.01 and 0.36 μg/mL).



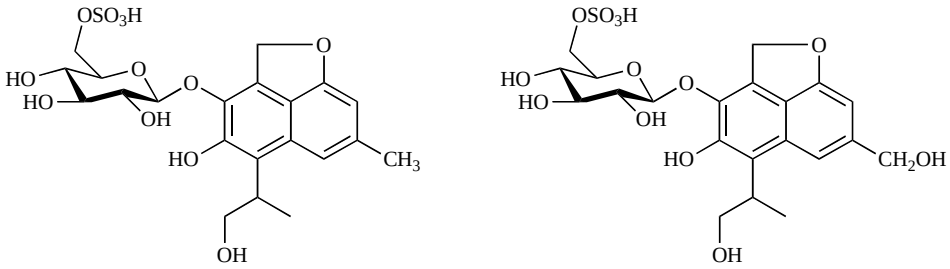
**62** **63** **64** **65** **66**

**Fig. (18).** Halogenated sesquiterpenoids **62-66**.



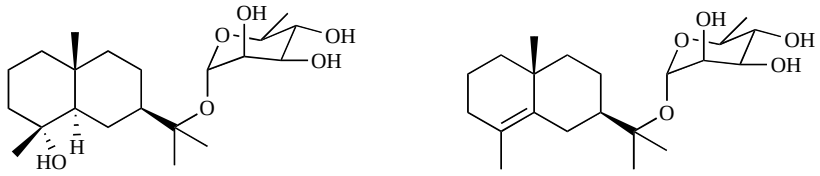
**67** **68** **69**

**Fig. (19).** Nakijiquinones G-I.



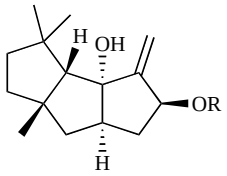
**70** **71**

**Fig. (20).** Sulfated cadinene-type sesquiterpenoid glycosides.



**72** **73**

**Fig. (21).** Eudesmane sesquiterpene glycosides.



**74:** R = H
**75:** R = benzoyl
**76:** R = 4-methylbenzoyl
**77:** R = 4-chlorobenzoyl
**78:** R = 2-furoyl
**79:** R = 4-fluorobenzoyl
**80:** R = 2-thiophenoyl
**81:** R = 4-propylbenzoyl
**82:** R = cinnamoyl
**83:** R = 4-nitrobenzoyl
**84:** R = 4-methoxybenzoyl

**Fig. (22).** Capnellenes-8β,10α-diol (**74**) and its acylation products **75-84**.

## 5. TRICYCLIC SESQUITERPENOIDS

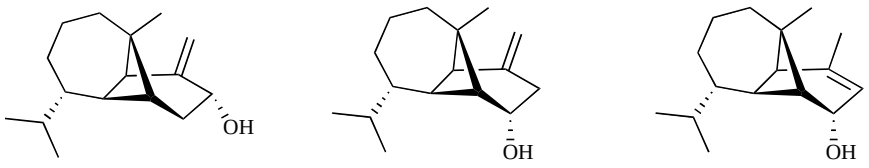
### 5.1. Sesquiterpenoid Alcohols and Esters

*Capnella* (Nephtheidae) is a widely distributed genus of Alcyonacea that provide nonisoprenoid sesquiterpenes with a 5-membered tricyclic skeleton named capnellane. The sesquiterpene capnellene-8β,10α-diol **74** (Fig. (**22**)) was isolated from non-polar extract of the soft coral *Capnella* sp [34]. Ten acylation products of **74** were prepared. The cytotoxic activities of compounds **74-84** were tested against human cervical epitheloid carcinoma (Hela), human oral epidermoid (KB), human medulloblastoma (Daoy), and human colon adenocarcinoma (WiDr) tumor cell lines. The results are summarized in Table **1**. All tested compounds showed significant cytotoxicity against Hela and KB cell lines with the exception of benzoyl ester **75**. Compounds **74** and **78** exhibited the strongest activity against the WiDr cell line with $IC_{50}$ 0.16 and 0.35 μg/mL, respectively, while compounds **76** and **84** showed moderate activity against the same cell line. Compounds **78** and **84** showed exclusive moderate cytotoxicity against the Daoy cell line, while all other compounds were inactive. The benzoyl ester **75** was inactive against all tested cell lines, but it seems that substitution at the *para*-position increased the cytotoxic activity, especially against Hela and KB cells. The activity of almost all esters against Hela and KB cells was superior compared to the parent compound **74**, especially in the case of **77**, **80**, and **84**. This may be attributed to greater penetration of the cytotoxic ester into the cancer cells.

**Table 1. Cytotoxic Activity of Compounds 74-84**

| Compound | IC50 (μg/mL) | | | |
|---|---|---|---|---|
| | Hela | KB | Daoy | WiDr |
| **74** | 3.56 | 6.06 | >20 | 0.16 |
| **75** | >20 | >20 | >20 | >20 |
| **76** | 3.13 | 5.45 | >20 | 8.00 |
| **77** | 2.36 | 2.19 | >20 | 10.50 |
| **78** | 3.05 | 4.10 | 9.93 | 0.35 |
| **79** | 2.70 | 2.48 | >20 | 15.93 |
| **80** | 2.49 | 2.09 | >20 | >20 |
| **81** | 4.79 | 3.86 | >20 | >20 |
| **82** | 3.02 | 2.77 | >20 | >20 |
| **83** | 3.10 | 2.96 | >20 | >20 |
| **84** | 2.63 | 1.92 | 5.42 | 6.30 |
| **Mitomycin C** | 0.09 | 0.08 | 0.07 | 0.06 |

The ylangene-type sesquiterpenoids, lemnalol (**85**), cervicol (**86**) and isolemnalol (**87**) (Fig. (**23**)), were isolated



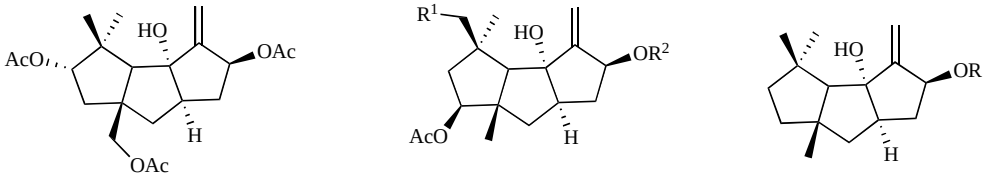

**85** **86** **87**

**Fig. (23).** Lemnalol, cervical and isolemnalol.

from the Formosan soft coral *Lemnalia cervicorni* [35]. Lemnalol (**85**) exhibited moderate cytotoxicity against P-388 and HT-29 with $ED_{50}$ values of 16.3 μM and 10.5 μM, respectively, while compounds **86** and **87** were inactive against these two cell lines ($ED_{50}$ >50 μM).

Capnellenes **88-93** (Fig. (**24**)) were isolated from the soft coral *Dendronephthya rubeola* [36]. Compounds **92** and **93** showed a good antiproliferative activity against the murine fibroblasts cell line L-929 ($GI_{50}$: 6.8 and 20.9 μM, respectively) and a good cytotoxic activity against the HeLa (human cervix carcinoma) cell line ($ED_{50}$: 7.6 and 9.6 μM, respectively). The antiproliferative and cytotoxic activity of dihydroxycapnellene **92** against L-929 and HeLa cells is 5.7 and 3.8 times lower, respectively, in comparison with doxorubicin which is used in the cancer therapy for the treatment of leukemia, lymphoma, sarcoma, and carcinoma. The universal deregulation of the c-myc gene expression in tumor cells suggests that this oncogene represents an attractive target for cancer-therapeutic purposes. The oncogenic transcription factor Myc forms complexes with its binding proteins Max and Miz-1. Inhibitors of this complex formation are compounds with potential antitumor activity. Capnellenes **88-93** were tested for their ability to inhibit the interaction of Myc with their partner proteins Max and Miz-1 in yeast two-hybrid assay. An interaction assay of the viral transcription factors Tax and CREB was used as a control. Only capnellene **92** showed a specific inhibition (77%) of the Myc/Max interaction in yeast and a significantly lower inhibition of the Myc/Miz-1 interaction (34%) and Tax/CREB interaction (27%). This specific inhibition of Myc/Max interaction well correlates with the antiproliferative activity of capnellene **92** against the L-929 cell line.

The illudins are a family of natural sesquiterpene compounds with antitumor activity. Illudin S (**94**) and illudin M (**95**) (Fig. (**25**)) are highly toxic sesquiterpenes found in the basidiomycete Omphalotus illudens [37, 38]. Illudin S had high activity against *Staphylococcus aureus* but was extremely toxic to animals. In the evaluation of illudins and their derivatives for antitumor activity in the National Cancer Institute Developmental Therapeutics Program, illudin M was found to significantly increase the life span of rats with Dunning leukemia but had a low therapeutic index in solid tumor systems [39, 40]. Because of their unacceptable toxicity, natural illudins are of limited interest as antitumor agents. In an attempt to exploit their cytotoxic potential, novel derivatives with a strongly improved therapeutic index have been synthesized. One of these, hydroxymethylacylfulvene (HMAF, Irofulven, **96**), is selected for clinical trials. In a randomized phase IIB clinical trial, irofulven significantly increased overall survival in patients with metastatic hormone-refractory prostate cancer who previously failed salvage treatment with docetaxotere [41]. The cytotoxic activities of illudins are related to their alkylating abilities. For the details of their action mechanism and the discovery and development of sesquiterpenoid derived hydroxymethylacylfulvene as a new anticancer drug, please refer to an excellent review by McMorris [42].

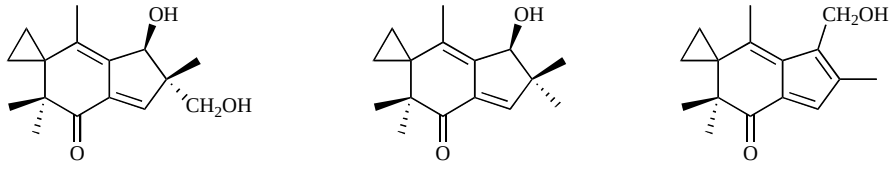



**88**

**89:** $R^1 = R^2 = OAc$
**90:** $R^1 = OAc$; $R^2 = H$
**91:** $R^1 = H$; $R^2 = OAc$

**92:** R = H
**93:** R = OAc

**Fig. (24).** Capnellenes **88-93**.

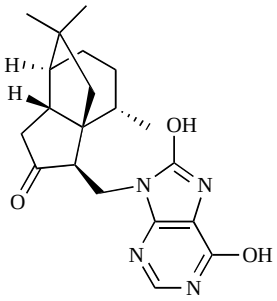



**94** **95** **96**

**Fig. (25).** Illudin S and M, irofulven.

### 5.2. Sesquiterpenoid Ketones

Sesquiterpenoid alkaloid **97** (Fig. (**26**)) was isolated from the $EtOH/CH_2Cl_2$ extracts of the South China Sea gorgonian *Subergorgia suberosa* [43]. It showed moderate cytotoxicity against the human breast carcinoma MDA-MB-231 cell line with an $IC_{50}$ of 8.87 μg/mL and potential cytotoxicity toward the MCF cell line at a concentration of 50 μM.



**97**

**Fig. (26).** Sesquiterpenoid alkaloid **97**.

## 6. CONCLUSION

In this review, we have provided a brief survey of the naturally occurring sesquiterpenes that have already displayed an intrinsic cytotoxicity against tumor cells of various types. Only a few of these compounds have already been studied extensively both *in vitro* and *in vivo* and shown to have high potency and specificity, many others continue to be fruitful subjects for investigation. Both biological evaluations and the synthesis of novel analogs of sesquiterpenes for the structure-activity relationship studies should be stressed in the future. The results of phase IIB clinical trials of semi-synthetic irofulven (**96**) are encouraging, and we believe that in the near future, many more derivatives of these naturally occurring sesquiterpenes will emerge as lead molecules and clinical agents. The age-old strategy of searching for compounds of natural origin will continue to yield rich dividends in the quest for specific and highly efficacious cytotoxic anticancer agents.

## ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (NSFC, Grant No. 81072517 and 30873134).

## ABBREVIATIONS

$ED_{50}$ = a concentration that caused 50% inhibition of cell growth *in vitro*

$IC_{50}$ = a concentration that resulted in a 50% decrease in cell number

$EC_{50}$ = half maximal effective concentration

$GI_{50}$ = a concentration that caused 50% growth inhibition

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Received: March 02, 2011 Revised: May 20, 2011 Accepted: June 15, 2011