The Chemical Investigations of the Mangrove Plant *Avicennia marina* and its Endophytes

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Abstract: A diverse array of bioactive compounds have been isolated and characterized from the mangrove plant *Avicennia marina* and its endophytes. Extensive chemical investigations of the different parts (barks, leaves, twigs, etc.) of the mangrove plant *A. marina* and its endophytes (mainly endophytic fungi) resulted in the reporting of the isolation of 123 compounds, and most of them are new or novel compounds. Most of compounds produced by the endophytes were different from the chemical components of the host *A. marina*, but it can still be found that some metabolites of the endophytes and some chemical components of the host possess the same structure unit. It suggested that there exist some biogenetic relationships between the endophytes and its host. Their biological activities, structural and stereochemical assignments are reported.

Keywords: *Avicennia marina*, mangrove, chemical component, endophyte, metabolite.

INTRODUCTION

Recently, it was found that the mangrove plants and its endophytes can produce lots of significant natural structures [1]. As a pioneer tree species of mangrove forest ecosystems, *Avicennia marina* belonging to the family Verbenaceae, is a cosmopolitan species widely distributed along tropical and subtropical coastlines. The barks, leaves, and fruits of this species have been used as traditional medicine in Egypt to treat skin diseases [2]. *A. marina* contains abundant chemical components. Since Bell *et al.* [3] reported the bark of *A. marina* contains triterpenoids (betulic acid 0.3%, taraxerol 0.06% and taraxerone 0.05%), and traces of hydrocarbon, lots of chemical components were isolated from the different parts of *A. marina* by natural chemists, especially it was found that lots of significant metabolites can be produced by its endophytes recently, which laid foundation for the exploitation of *A. marina*. Here, the chemical components isolated from the plant and the metabolites produced by its endophytes were reviewed.

CHEMICAL INVESTIGATIONS OF *AVICENNIA MARINA*

Terpenoids and Steroids

Many terpenoids and steroids exist in the barks [3], leaves [4-6], flowers [7], fruits [8] of *A. marina* were identified by HPLC, GC or GC-MS technique. Jia *et al.* [9] reported the isolation of lupeol (**1**), betulin (**2**), *β*-sitosterol (**3**) and ergost-6,22-diene-5,8-epidioxy-3*β*-ol (**4**), from the leaves of *A. marina* collected in Beihai, Guangxi province, P. R. China. From the leaves collected in Hainan province, Feng *et al.* [10] also isolated lupeol and betulin, and another terpenoid, betutinic acid (**5**).

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Recently, Han *et al.* [11] reported that the twigs of *A. marina* growing at Xiamen, P. R. China yielded two new abietane diterpenoids, a pair of inseparable epimers 6H*α*-11,12,16-trihydroxy-6,7-secoabieta-8,11,13-triene-6,7-dial 11,6-hemiacetal (**6**) and 6H*β*-11,12,16-trihydroxy-6,7-secoabieta-8,11,13-triene-6,7-dial 11,6-hemiacetal (**7**), as well as 6,11,12,16-tetrahydroxy-5,8,11,13-abitetetraen-7-one (**8**). Compounds **6**-**8** showed moderate cytotoxic and antimicrobial activities.

Naphthalene Derivatives

Sutton *et al.* [12] reported that infection of wound tissue of *A. marina* seedlings by a fungus belonging to the genus *Phytophthora* induced the production of three chemically-related naphthofuranone phytoalexins. One was identified as naphtha[1,2-b]furan-4,5-dione (**9**), and the other two tentatively as 3-hydroxy-naphtha[1,2-b]furan- 4,5-dione (**10**) and 2-[2′-(2′-hydroxy)propyl]-naphtha[1,2-b]furan-4,5-dione (**11**). These components present in the extract of the inoculated tissue were found to be inhibitory to the growth of *Phytophthrora* sp. *in vitro* bioassay, and accounted for nearly all of the activity of the extract.

From the leaves of *A. marina* collected in Beihai, Guangxi province, Jia *et al.* [9] also isolated two naphthoquinone derivatives identified as avicequinone B (**12**) and avicequinone C (**13**). In 2007, Han *et al.* [13] reported seven unusual naphthoquinone derivatives were isolated from the twigs of *A. marina* collected in Xiamen province, namely, avicennone A-G (**14**-**20**), along with the known compounds avicequinone A (**21**), stenocarproquinone B (**22**), avicequinone C (**13**), avicenol A (**23**), and avicenol C (**24**). Compounds **13**, **21**, **22** and a mixture of **17** and **18**, which contain a 4,9-dione group, showed strong antiproliferative and moderate cytotoxic activities, as well as antibacterial effects. The new ligan, (7′*S*, 8′*R*)-4,4′,9′-trihydroxy-3,3′,5,5′- tetramethoxy-7,8-dehydro-9-al-2,7′-cycloligan (**25**), together with the

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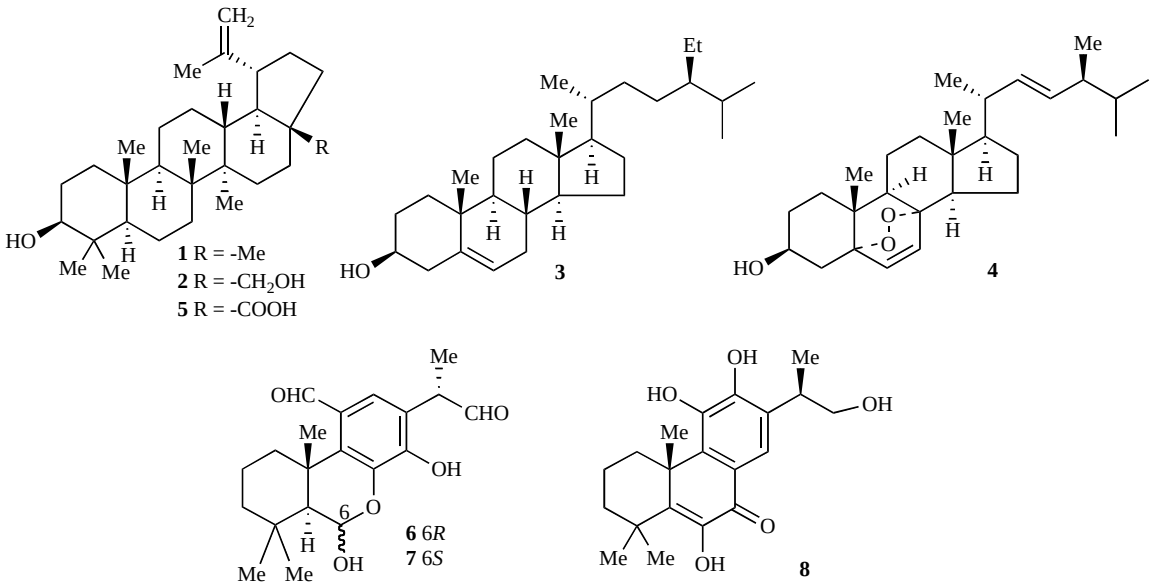


Fig. (1). Terpenoids and steroids from *Avicennia marina.*

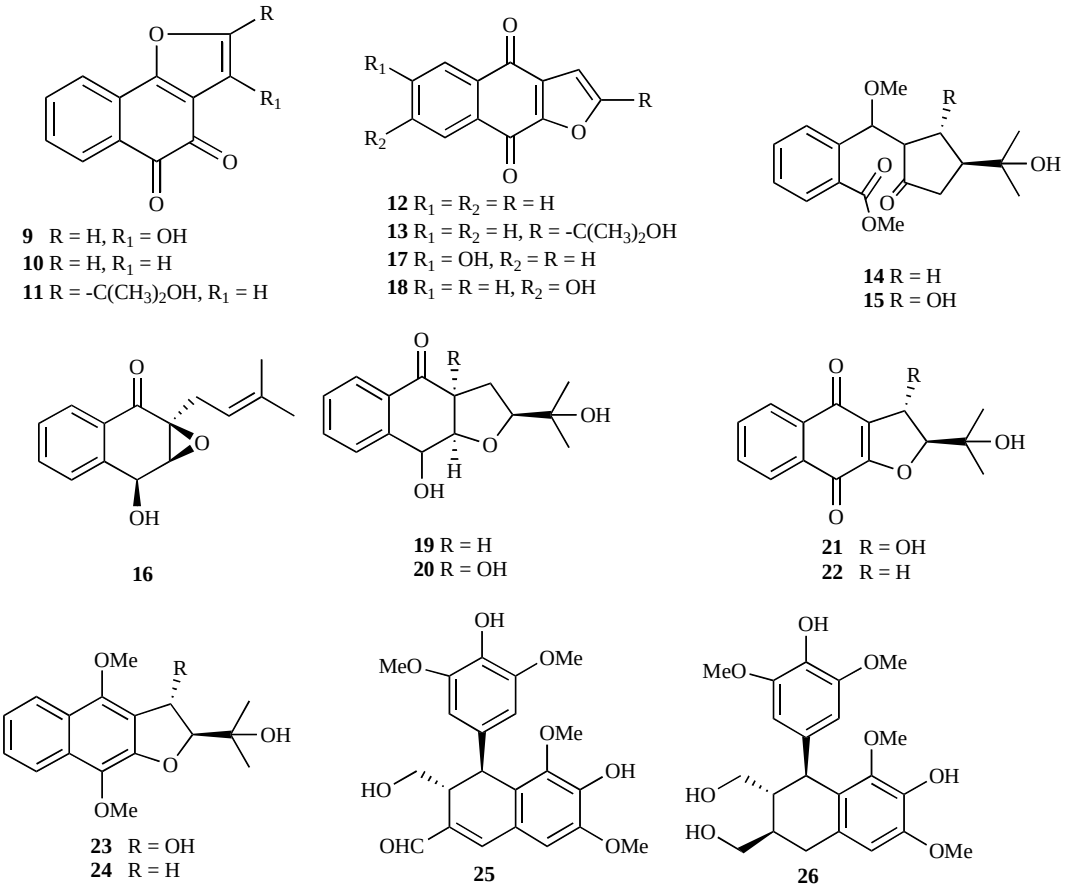


Fig. (2). Naphthalene derivatives from *Avicennia marina.*

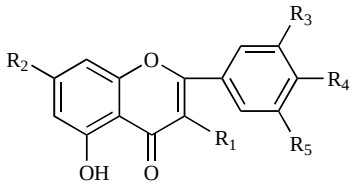
known compound, lyoniresinol (**26**), were also isolated by Han *et al.* [11] from the twigs.

Flavones

Sharaf *et al.* [14] isolated a flavone, luteolin 7-*O*-methylether (**27**), from *A. marina* aerial parts collected from Abu-Ramad, 500 km south of Hurghada (Red Sea shore), and found it showed moderate cytotoxity against BT-20 human carcinoma cells with ED_{50} of 18 μg/mL.

Jia *et al.* [9] also obtained three flavones from the leaves, and identified them as 5-hydroxy-4′, 7-dimethoxyflavone (**28**), quercetin (**29**) and kaempferol (**30**). Four known flavones including 4′,5-dihydroxy-3′,7-dimethoxyflavone (**31**), 4′,5-dihydroxy-3′,5′,7-trimethoxyflavone (**32**), 4′,5,7-

trihydroxyflavone (**33**), and 3′,4′,5-trihydroxy-7-methoxyflavone (namely **27**) were isolated by Feng *et al.* [15] from the aerial parts of *A. marina* collected in Hainan island of South China Sea. The scavenging activity of them was evaluated using the *α,α*-diphenyl-*β*-picrylhydrazyl (DPPH) radical-scavenging assay. Compounds **31** and **32** showed only weak activities, while compounds **33** and **27** showed moderate activities, with IC_{50} of 52.0 and 37.0 μg/mL, respectively. Another flavone, 5,7-dihydroxy-3′,4′,5′-trimethoxyflavone (**34**), was also isolated by them [10] later.



27 $R_1 = R_5 = H$, $R_2 = OMe$, $R_3 = R_4 = OH$
28 $R_1 = R_3 = R_5 = H$, $R_2 = R_4 = OMe$
29 $R_1 = R_2 = R_3 = R_4 = OH$, $R_5 = H$
30 $R_1 = R_2 = R_4 = OH$, $R_3 = R_5 = H$
31 $R_1 = R_5 = H$, $R_2 = R_3 = OMe$, $R_4 = OH$
32 $R_1 = H$, $R_2 = R_3 = R_5 = OMe$, $R_4 = OH$
33 $R_1 = R_3 = R_5 = H$, $R_2 = R_4 = OH$
34 $R_1 = H$, $R_2 = OH$, $R_3 = R_4 = R_5 = OMe$

Fig. (3). Flavones from *Avicennia marina.*

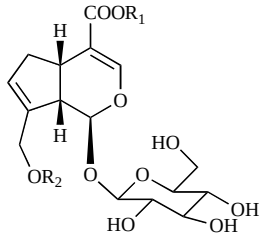
Glucosides

1. Iridoid Glucosides

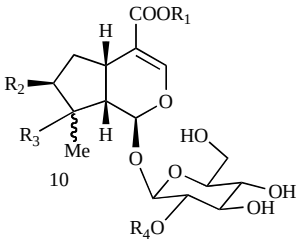
It has been reported that there is no general agreement on the taxonomy of the mangrove plant genus *Avicennia*. The genus is considered either as a member of the family Verbenaceae or the family Avicenniaceae. The metabolism of iridoids of dicotyledons has been considered as an important taxonomic character.

In 1985, König *et al.* [16] reported that seven iridoid glucosides were isolated from a methylated extract of the leaves of *A. marina* obtained from wild growing plants in Ceylon. These iridoids glycosides are geniposidic acid (**35**), 2′-cinnamoyl-mussaenosidic acid (**36**), geniposide (**37**), mussaenoside (**38**), 2′-cinnamoyl-mussaenoside (**39**), 10-*O*-(5-phenyl-2,4-pentadienoyl)-geniposide (**40**), 7-*O*-(5-phenyl-2,4-pentadienoyl)-8-epiloganin (**41**), respectively. Evidence is presented that the iridoids occur as the free acids in the plant. They pointed out that the accumulation of iridoids in this species indicated a fairly close relationship between the genus *Avicennia* and the family Verbenaceae.

In 2001, Shaker *et al.* [17] isolated three new iridoid glucosides, 10-*O*-[(E)-cinnamoyl]-geniposidic acid (**42**), 10-*O*-[(E)-*p*-coumaroyl]-geniposidic acid (**43**), 10-*O*-[(E)-caffeoyl]-geniposidic acid (**44**) and the known iridoid glucoside, 2′-*O*-[(E)-cinnamoyl]mussaenosidic acid (**36**) from *A. marina*. In 2006, Feng *et al.* [15, 18] obtained two new iridoid glucosides, namely, 2′-*O*-[(2E,4E)-5-phenylpenta-2,4-dienoyl]mussaenosidic acid (**45**) and 2′-*O*-(4-mehtoxycinnamoyl)mussaenosidic acid (**46**) , together with a known iridoid glucoside, 2′-*O*-coumaroylmussaenosidic acid (**47**), from the aerial parts of *A. marina*. Compounds **45** - **47** showed weak radical scavenging activity to DPPH. In 2008, Sun *et al.* [19] reported that the isolation and characterization of five new iridoid glucosides, marinoids A - E (**48** - **52**), along with the known iridoid glucosides **36**, **46** and **47** from the leaves of *A. marina* collected in the coast of Xiamen, Southern China. They pointed out that the iridoid glucosides in the leaves of plant *A. marina* may play a role for chemical defense against ecological invasion.



35 $R_1 = R_2 = H$
37 $R_1 = Me$, $R_2 = H$
40 $R_1 = Me$, $R_2 =$ (2E,4E)-5-phenyl-2,4-pentadienoyl
42 $R_1 = H$, $R_2 =$ (E)-cinnamoyl
43 $R_1 = H$, $R_2 =$ (E)-*p*-coumaroyl
44 $R_1 = H$, $R_2 =$ (E)-caffeoyl
51 $R_1 = H$, $R_2 =$ 4-hydroxy-3,5-dimethoxybenzoyl
52 $R_1 = H$, $R_2 =$ 3(*R*)-hydroxy-5-phenyl-4(E)-pentenoyl



36 $R_1 = R_2 = H$, $R_3 = OH$, $R_4 =$ (E)-cinnamoyl, Me-10alpha
38 $R_1 = Me$, $R_2 = R_4 = H$, $R_3 = OH$, Me-10alpha
39 $R_1 = Me$, $R_2 = H$, $R_3 = OH$, $R_4 =$ (E)-cinnamoyl, Me-10alpha
41 $R_1 = Me$, $R_3 = R_4 = H$, $R_2 =$ (2E,4E)-5-phenyl-2,4-pentadienoyl, Me-10alpha
45 $R_1 = R_2 = H$, $R_3 = OH$, $R_4 =$ (2E,4E)-5-phenyl-2,4-pentadienoyl, Me-10alpha
46 $R_1 = R_2 = H$, $R_3 = OH$, $R_4 =$ (E)-4-methoxycinnamoyl, Me-10alpha
47 $R_1 = R_2 = H$, $R_3 = OH$, $R_4 =$ (E)-*p*-coumaroyl, Me-10alpha
48 $R_1 = R_2 = H$, $R_3 = OH$, $R_4 =$ (E)-cinnamoyl, Me-10beta
49 $R_1 = R_2 = H$, $R_3 = OH$, $R_4 =$ (E)-4-methoxycinnamoyl, Me-10beta
50 $R_1 = R_2 = H$, $R_3 = OH$, $R_4 =$ (E)-*p*-coumaroyl, Me-10beta

Fig. (4). Iridoids glucosides from *Avicennia marina.*

2. Phenylpropanoid Glycosides

Fauvel *et al.* [2] isolated three phenylpropanoid glycosides from the methanol extracts of *A. marina* leaves. They were identified as verbascoside (**53**), isoverbascoside (**54**) and derhamnosylverbascoside (**55**). Compounds **53** and **54** were also isolated by Feng *et al.* [10] from the leaves of *A. marina* collected in Hainan province. In 2008, Han *et al.* [11] also reported the isolation of diacetaylmartynoiside (**56**) from the twigs.

3. Flavonoids

In 2000, Sharaf *et al.* [14] found the methanol extract of the aerial parts of *A. marina* yielded four flavonoids, namely, chrysoeriol 7-*O*-glucoside (**57**), isorhamnetin 3-*O*-rutinoside (**58**), luteolin 7-*O*-methylether 3′-*O*-*β*-D-glucoside (**59**) and its galactoside analogue (**60**). Compounds **59** and **60** are new flavonoids. Compound **59** showed moderate cytotoxic against BT-20 human carcinoma cells with ED_{50} of 16 μg / mL.

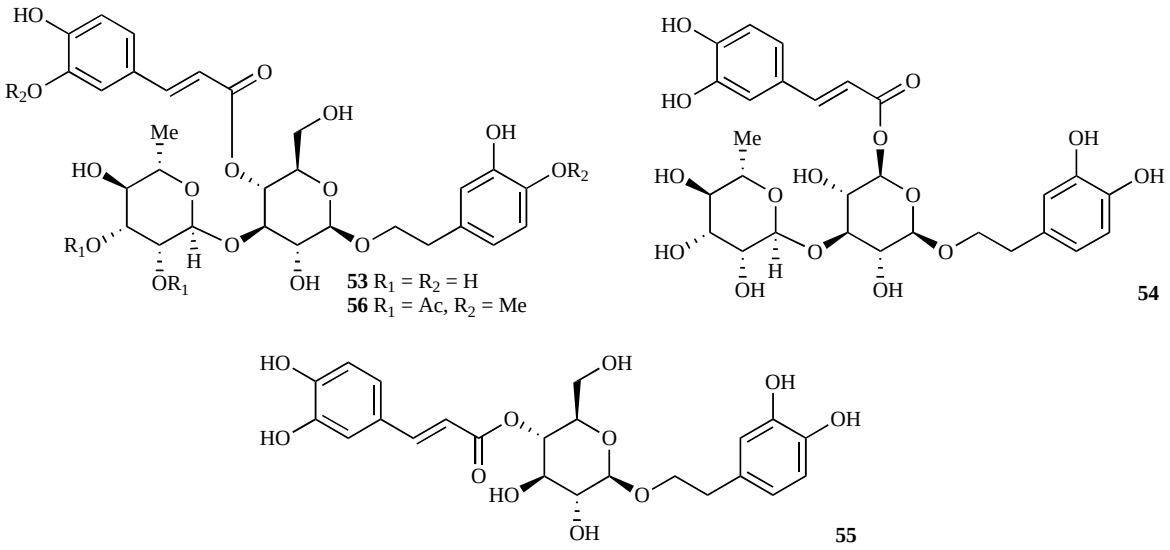


Fig. (5). Phenylpropanoid glycosides from *Avicennia marina*.

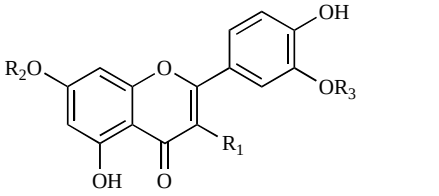


Fig. (6). Flavonoids from *Avicennia marina*.

4. Abietane Diterpenoid Glucosides

A new abietane diterpenoid glucoside, 11-hydroxy-8,11,13-abietatriene 12-*O*-*β*-xylopyranoside (**61**), and a known compound lyoniresinol 9′-*O*-*β*-D-glucopyranoside (**62**) were isolated by Han *et al.* [11] from the twigs of *A. marina*.

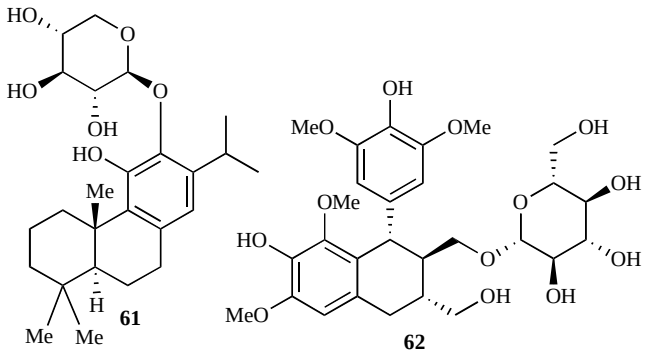


Fig. (7). Abietane diterpenoid glucosides from *Avicennia marina.*

The Others

Two biosynthesis precursors for iridoids were also isolated from *A. marina*, namely, *p*-methoxy cinnamic acid (**63**) obtained by Jia *et al.* [9], and 3(*R*)-hydroxy-5-phenyl-4(E)-pentanoic acid (**64**) obtained by Sun *et al.* [19]. Syringaresinol (**65**) and indolyl-3-carboxylic acid (**66**) were isolated by Feng *et al.* [10]. Compound **66** is the only one alkaloid isolated from *A. marina*.

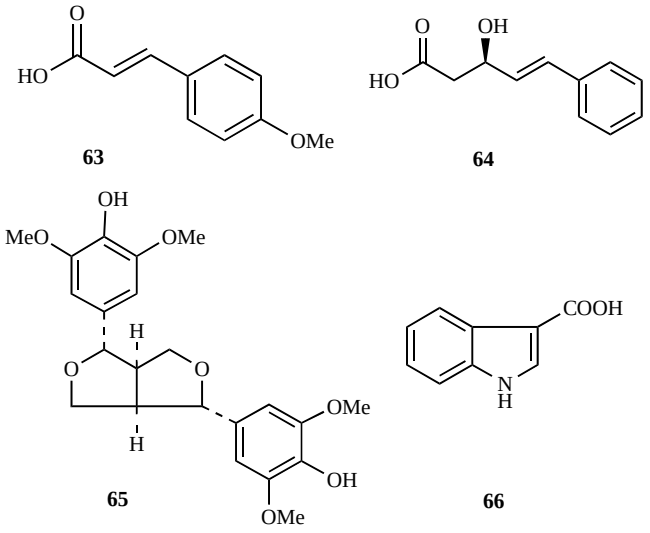


Fig. (8). The other chemical components from *Avicennia marina.*

CHEMICAL INVESTIGATIONS OF THE ENDOPHYTES OF *AVICENNIA MARINA*

The mangrove habit has proved to be a rich source of new fungal species, and these now form the second largest ecological sub-group of marine fungi. Endophytes are defined as fungi colonizing healthy plant tissue without causing overt symptoms in or apparent injury to the host. Research on the metabolites of endophytes can reveal the relationship between them and their hosts. Zheng *et al.* [20], Deng *et al.* [21], Tariq *et al.* [22] and Chen *et al.* [23] reported the isolation of fungi from *A. marina*, and found most of them showed antibacterial or antitumor activities.

Xyloketals, Xyloallenolides and its Precursors

Xyloketals are most interesting ketals produced by the endophytic fungus *Xylaria* sp. (No. 2508) from the seeds of

A. marina in Mai Po, Hong Kong. In the previous study, the fungus was shown to produce xyloketals A-I (**67**-**75**) [24-28] and xyloallenolide A (**76**) [29], two chemical families with novel frameworks, and exhibited strong activity against L-calcium channels and inhibition of acetylcholine esterase. Subsequently, fermentation of the fungus in large scale yielded three metabolites [30], named xyloketal J (**77**), xyloester A (**78**), and xyloallenolide B (**79**) (which belong to a new series of compounds), and a known substituted dihydrobenzofuran (**80**). It was found that xyloketal C (**69**) slowly rearranged to xyloketal B (**68**) in DMSO-d_6 solution at room temperature. Compound F (**72**) also can be synthesized by condensation of xyloketal B (**68**) with formaldehyde. It is biogenetically interesting that compounds **77**, **78**, and **79** possess a substituted dihydrobenzofuran unit (**80**).

In addition, two aromatic allenic ethers (**81** and **82**) [29] and five phenols (**83**-**88**) [24, 31, 32] were also produced by the fungus. Compounds **85** and **88** belong to isocoumarin.

Cyclic Peptides

The previous compound xyloallenolide A (**76**) is a novel cyclic peptide containing an allenic ether of a *N*-(*p*-hydroxycinnamoyl)amide. Li *et al.* [33, 34] isolated five cyclic dipeptides, namely cyclo-(Tyr-Leu) (**89**), cyclo-(Phe-Ala) (**90**), cyclo-(Ala-Val) (**91**), cyclo-(Pro-Gly) (**92**) and 5-isobuty1-2,4-imidazolidinedione (**93**), and one new cyclic pentapeptide, cyclo-(*L*-Phe-*L*-Leu^1-*L*-Leu^2-*L*-Leu^3-*L*-Ile) (**94**), from the fungus (No. 2524) isolated from a seed of *A. marina* from Hong Kong. Compound **94** exhibits inhibitory activity against human heptoma cell line Bel-7402. The cellular livability was 67% at the dose of 15 μg / mL. However, no dose-related effects were observed for dosages between 15 and 500 μg / mL. Other results showed that these compounds do not exhibit significant cytotoxicity. Generally, most cyclopeptides or cyclic depsipeptides from microorganisms presented D-amino acids or unusual amino acids. They often possess unusual pharmacological properties, including as antibiotics, toxins, immunosuppressants and ion transport regulators. However, the cyclic peptide **94** is composed of only the usual L-amino acids residues with hydrophobic side chains. Its simple architecture may explain the absence of potent cytotoxicity.

Zhu *et al.* [35, 36] also isolated four cyclic dipeptide, cyclo-(Tyr-Leu) (**89**), uracil (**95**) and cyclo-(Phe-Phe) (**96**)

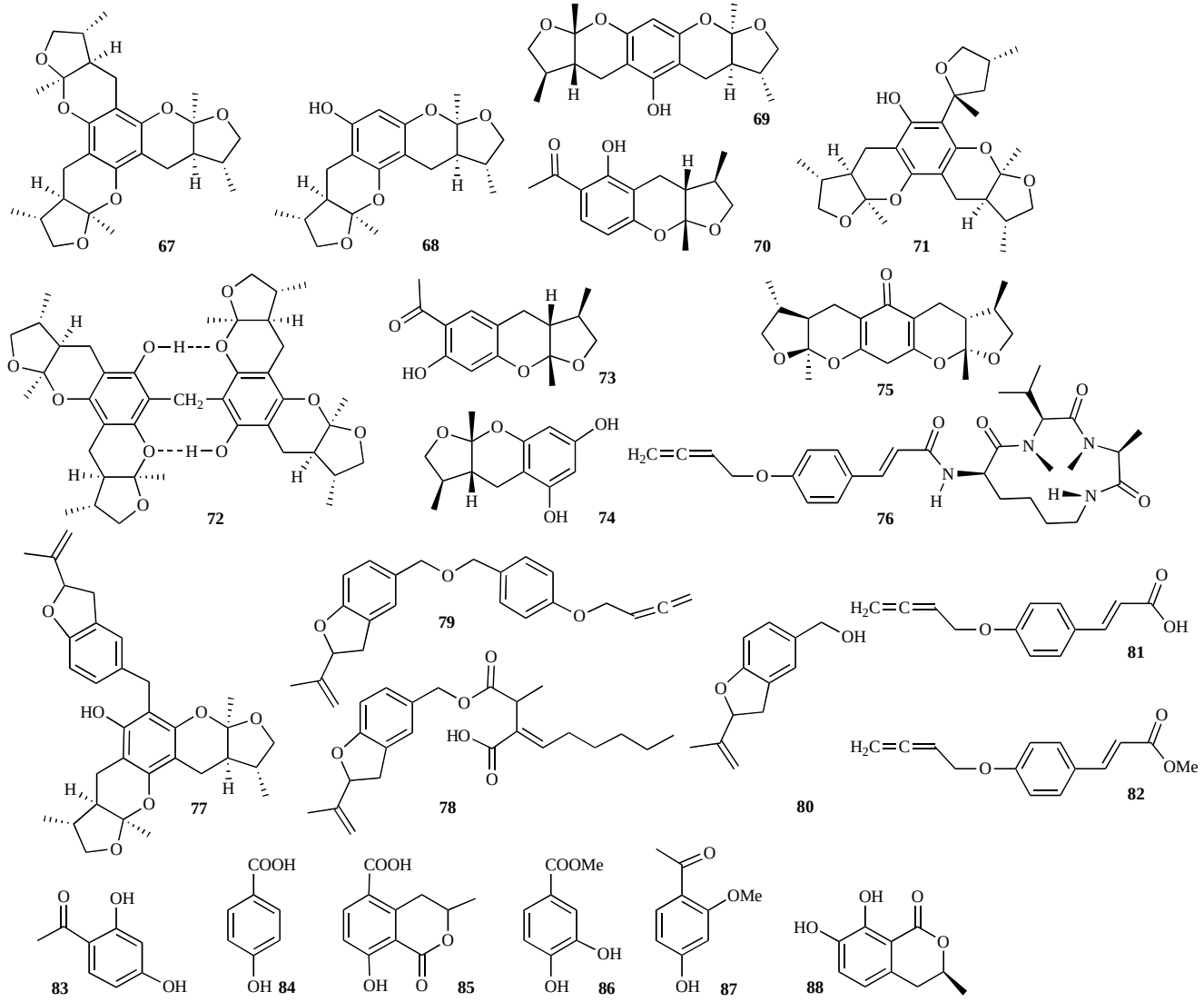


Fig. (9). Xyloketals, xyloallenolide and its precursors from endophytes.

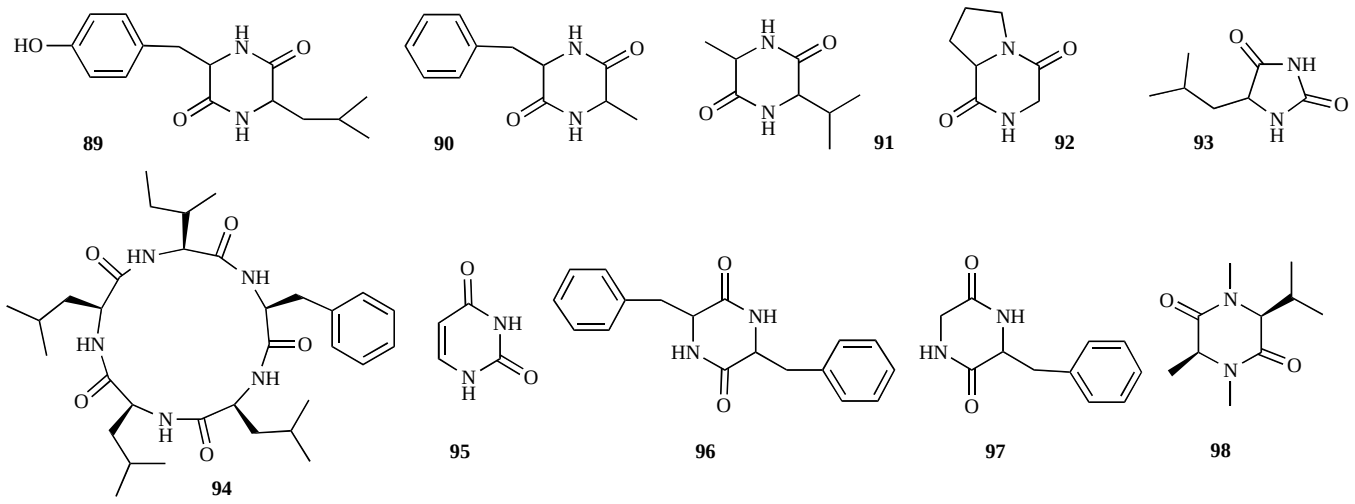


Fig. (10). Cyclic peptides from the endophytes.

from the endophytic fungus No. 2534, and cyclo-(Phe-Gly) (**97**) from the fungus No. 2526. Wang *et al.* [37] isolated a new cyclic dipeptide, cyclo-(*N*-MeVal-*N*-MeAla) (**98**), from the fungus No. 2106 from the seeds of *A. marina* in Hong Kong. The *N*-methyl cyclic dipeptide structure is uncommon in nature.

Sphingolipids

Sphingolipids are the major lipid components of biological membranes. They serve as structural support and shape determinants of the cell membrane and, *via* protein binding, act as mediators of biological events such as activation, cell agglutination, intracellular communication, cell death, and cell growth. [38]

Li *et al.* [39] isolated two new ceramides, [2′,3′-dihydroxytetracosanolyamino]-1,3-dihydroxy-octadecane (**99**) and [2′,3′-dihydroxydocosanoylamino]-1,3-dihydroxy-octadecane (**100**), from the culture extract of an unidentified endophytic fungus (strain No. 2524) separated from the seed of mangrove *A. marina* of Hong Kong. These two ceramides didn't exhibit significant cytotoxicity against the human hepatoma cell lines Bel-7402, NCI-4460 and the normal human cell lines L-02 in the preliminary cytotoxic activity investigation.

Zhu *et al.* [36, 40] found the fungus No. 2526 also can produce the ceramide **99**, and can produce other two ceramides, *N*-(2′,3′-dihydroxytetracosyl)-1,3-dihydroxy-2-amino-octadecane (**101**) and *N*-(2′,3′-dihydroxyhexacosyl)-1,3-dihydroxy-2-amino-octadecane (**102**), and two glycosphingolipids, 2′-dehydroxycerebroside D (**103**) and cerebroside D (**104**). Two ceramides and one glycosphingolipid, were isolated by Zhu *et al.* [41] from the fungus No. 2534 from the seeds of *A. marina*. Their structures were tentatively elucidated as *N*-hexacosyl-2-amino-1,3-dihydroxyoctadecane (**105**), *N*-(2-hydroxyeicosyl)-2-amino-1,3,4-trihydroxyoctadecane (**106**) and *N*-heneicosanoyl-2-amino-1-*O*-β-D-glucopyranosyl-3,4-dihydroxyoctadecane (**107**), respectively.

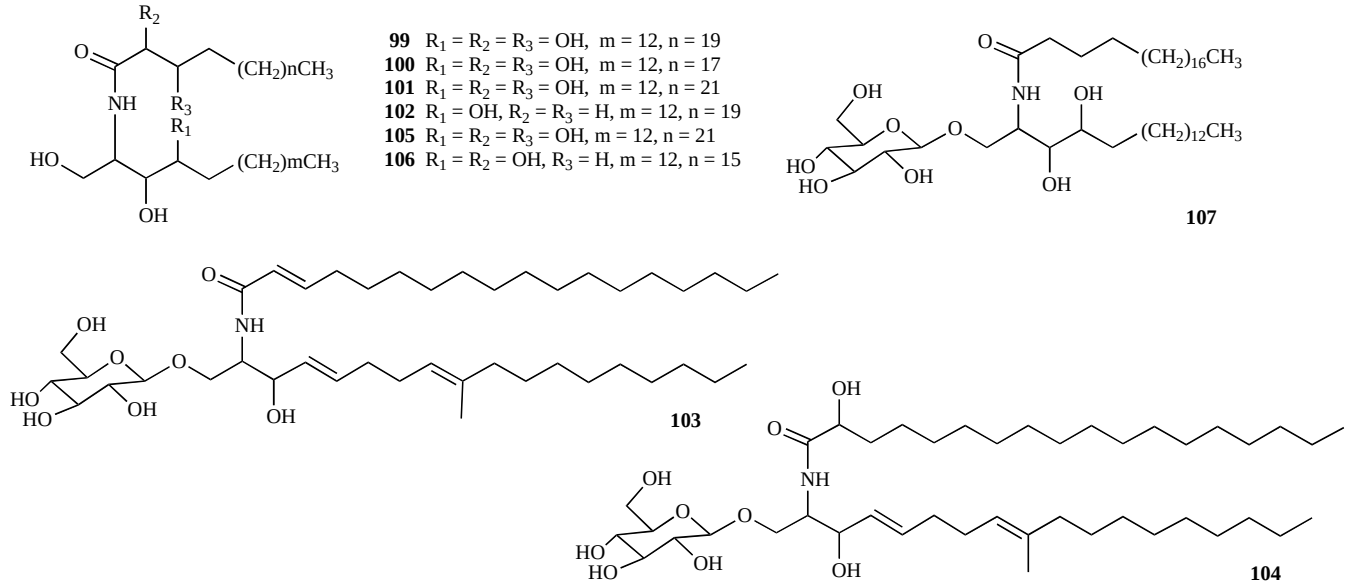


Fig. (11). Sphingolipids from the endophytes.

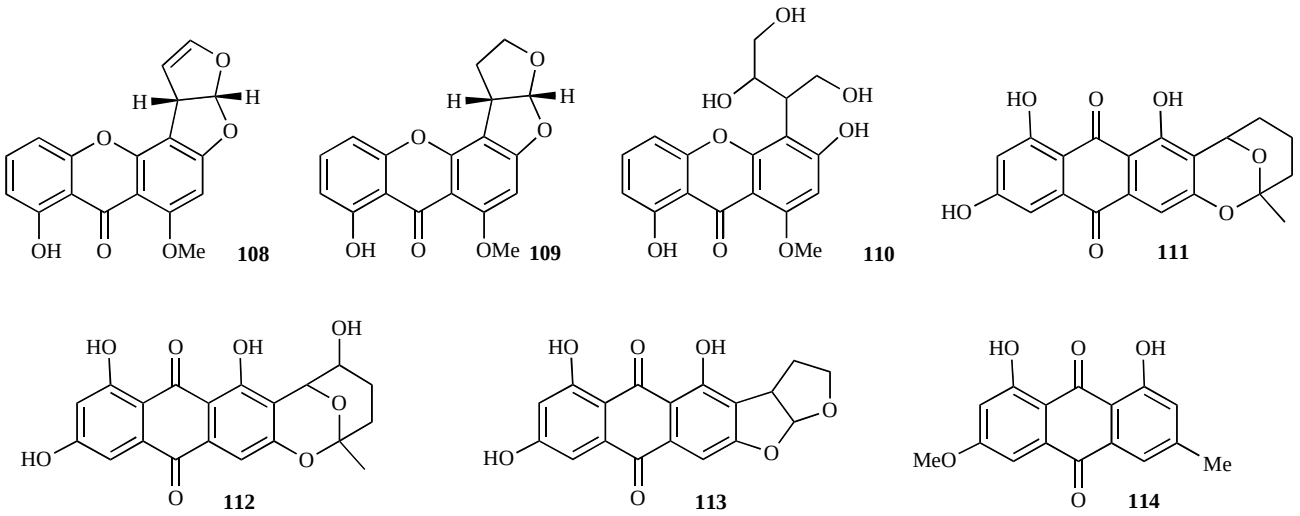


Fig. (12). Xanthones and anthraquinones from the endophytes.

Xanthones and Anthraquinones

The fungus No. 2526 which was isolated from a petiole of *A. marina* in Hong Kong was shown to also produce xanthones and anthraquinones, two chemical families with biosynthesis correlations. In the previous study [42], the fungus was shown to produce sterigmatocystin (**108**). Subsequently, fermentation of the fungus in large scale yielded the other two xanthones [43], dihydrosterigmatocystin (**109**) and secosterigmatocystin (**110**), and four anthraquinones [44], namely averufin (**111**), nidurufin (**112**), versicolorin C (**113**) and physicion (**114**). Secosterigmatocystin is a dominance secondary metabolite isolated from the fermentation liquid. The others are isolated from the mycelium. Sterigmatocystin is a dominance metabolite among them. Compound **109** and **110** seems to be derived from the enzymatic hydrogenation and the enzymatic degradation of sterigmatocystin. Anthraquinones **111**-**113** had been proved to be biosynthetic intermediates for sterigmatocystin.

Steroids, Esters, Lactones and the Others

Three steroids, namely ergost-6,22-diene-5,8-epidioxy-3β-ol (**4**), ergosterol (**115**) and cerevisterol (**116**) were produced by the fungi Nos. 2534 [35], 2526 [36], 2508 [31] and 2106 [37]. But only compound **4** were also found to be existed in the leaves of *A. marina*. Four esters, α-glycerol monopalmitate (**117**) [31], (3*S*,4*R*)-dihydroxy-(6*S*)-undecylapyranone (**118**) [34], no. 2106A (**119**) [37] and cytosporone B (**120**) [45] were also found produced by the fungi from *A. marina*. Among them, compunds **118** and **119** are new lactones. Compound **120** was produced by the endophytic fungus *Dothiorella* sp. HTF3 which was isolated from *A. marina* at the estuary of Jiulong River, Fujian Province, and showed high antitumor activities and broad antifungi spectra.

In addition, piliformic acid (**121**) [31], 9-oxo-stearic acid (**122**) [36] and mannitol (**123**) [36, 37], was produced by the fungal strains No. 2508, 2526 and 2106, respectively.

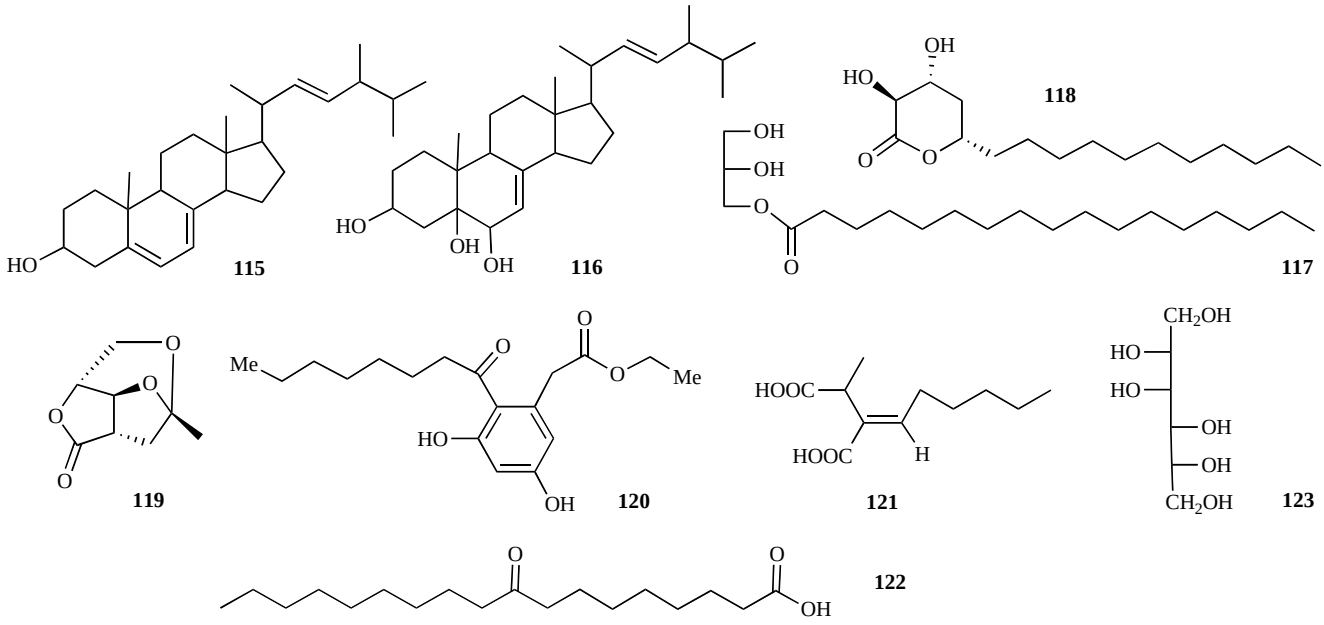
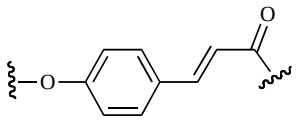


Fig. (13). Steroids, esters, lactones and the others metabolites from endophytes.

CONCLUSIONS

To date, sixty-six chemical components were isolated from the different parts of *A. marina*, and fifty-seven metabolites were obtained from its endophytes. Although lots of compounds produced by the endophytes were not found to be existed in the host *A. marina*, except compound **4,** it can still be found that xyloallenoide A (**76**), aromatic allenic esters (**81** and **82**) from the endophyte and some glucosides from the host all possess the same structure unit (**124**). It suggested that they all use the same compound as biosynthetic precursor.



124

Fig. (14). The same structure unit in some compounds from *Avicennia marina* and its endophytes.

Certainly only six endophytic fungal strains of *A. marina* have been chemically investigated, they are only a very small part of the endophytes of *A. marina* and therefore represent great potential for the discovery of new pharmacologically active metabolites. With the deep chemically investigation on the endophytes of *A. marina*, the relationship between the endophytes and its host *A. marina* would be revealed completely in the future.

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