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# Prenylation of Natural Products: An Overview

*Kantharaju Kamanna and Aravind Kamath*

## Abstract

Natural products with varied functional attributes are available in large abundance in nature. Nature has been an infinite repository of resources leading to drug development, discovery of novel chemicals, pharmacophores, and several invaluable bioactive agents. Natural products play a critical role in modern drug development, especially for antibacterial and antitumor agents. Their varied chemical structure, composition, solubility, and synthetic pathways bestow upon them a high level of diversity. Prenylation is a covalent addition of hydrophobic moieties to proteins or any other chemical compounds. Generally, the hydrophobic moieties are farnesyl or geranylgeranyl isoprenyl groups. Prenylation of flavonoids, alkaloids, terpenoids, etc., leads to gain of varied functionalities to the natural products in addition to the already existing functions. The ever-increasing need for the discovery of new drugs finds a new avenue through the prenylation of natural products. Cell-free synthesis of the prenylated natural products can be seen as a new alternative for the natural synthesis, which warrants time-consuming isolation and purification techniques.

**Keywords:** prenylation, natural products, antibacterial, antitumor

## 1. Introduction

Anything that is produced by life including biotic materials such as silk, hair, bio-based materials such as bioplastics, cornstarch, bodily fluids such as blood, milk, and other natural materials that were once found in living organisms such as shell, soil, coal, can all be called as natural products. They are products from various natural sources such as plants, microbes, and animals. The whole of the organism, a part of an organism, an extract from an organism, or pure compounds isolated from the organisms such as alkaloids, coumarins, flavonoids, steroids, lectins, lignans, terpenoids, nonribosomal polypeptides, and polyketides can all be termed as natural products. A limited scope of the definition of natural product can be any molecule synthesized by a living organism. Organic chemistry as we know today has its roots in the study of natural products. The semisynthetic chemistry is an offshoot of organic chemistry wherein the natural products are modified to alter/improve and enhance their activities.

The natural selection and evolutionary processes over millions of years have bestowed the natural products with high structural diversity and unique pharmacological or biological activities. Natural products exhibit structural diversity that is

far exceeding the variety that could be synthesized in a laboratory. Classification of natural products is often based on their biological function, biosynthetic pathway, or their source. Primary metabolites and secondary metabolites are the two major classes of natural products. The substances required for an organism to survive are termed as primary metabolites, whereas the substances that are not required for an organism to survive are termed as secondary metabolites. Secondary metabolites confer the organism with advantage in growth and survival within its environment. In practice, the term natural products generally refers to the secondary metabolites and small molecules with molecular weight < 1500 amu.

Natural products have been used for medicinal purposes since ancient times as herbal remedies. Natural products and their structural analogues have a strong impact on human culture and have been used throughout human history as condiments, pigments, and pharmaceuticals. Many of the natural products are potential drug candidates due to the prevailing increased antibiotic resistance. In comparison to the standard combinatorial chemistry, the natural products provide distinct structural diversity and functions. Limited by the lack of cost-effective production methodologies, the study and therapeutic potential of natural products have not been optimally explored. The similarities in the structures and variation in the sources of isolation make it difficult to isolate the natural products. The challenges associated with isolation/production of natural products are circumvented by development of several semisynthetic chemical syntheses.

Due to the safety and efficacy of the natural products, they have been the drugs of choice in improving the human health despite facing a tough competition from compounds derived from computational and combinatorial chemistry. Their importance in drug discovery has been enhanced owing to their largely untapped structural diversity [1]. Natural products containing prenyl side chains represent a rare class in themselves. For several decades now prenylated natural products are recognized as interesting and valuable biologically active phytochemicals [2]. Simple modifications by biological or chemical approaches produce a variety of prenylated aromatic compounds with added structural diversity, altered biological activity, and enhanced therapeutic potential.

A covalent addition of any hydrophobic moiety to protein or any other chemical compound can be termed as prenylation. In case of proteins, generally it is the addition of farnesyl or geranylgeranyl moiety to the cysteine residue via a thioester linkage at the C-terminus. This addition of prenyl moiety bestows novel hydrophobic properties on proteins that leads to the localization of prenylated proteins to the plasma membrane or organellar membranes. It has been shown that well-characterized prenylated proteins are major players in most of the cell signal transduction pathways.

Prenylation of natural products enhances various biological activities as compared with the respective nonprenylated compounds. Due to their versatile and promising pharmacological properties and health benefits on multitarget tissues, the prenylated forms have gained prominence [3, 4]. The increased lipophilicity of prenylated natural products as compared with nonprenylated forms leads to high affinity with cell membranes and enhanced biological activities or significant pharmacological effects [4, 5]. A multitude of biological activities offered by these compounds justifies their enhanced pharmacological investigation. Recent in-depth investigation of prenylated natural compounds with the prenyl substituents playing a key role in the molecular activity has led to discovery of promising anticancer, anti-inflammatory, antioxidant, and neuroprotective compounds. The prenylation of natural compounds is catalyzed by the several enzyme groups of prenyltransferases (PTases), including

membrane-embedded UbiA-type, bacterial and fungal ABBA-type, and fungal dimethylallyl tryptophan synthase (DMATS)-type PTases [6–8].

## 2. Different classes of natural products

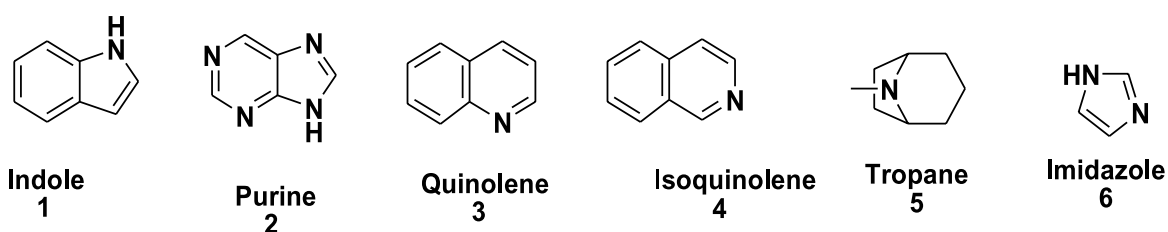
Natural products belong to several different classes of molecules. On the basis of their biosynthetic origin, they can be classified as: alkaloids, phenylpropanoids, polyketides, and terpenoids. Prenyl groups appear in a wide variety of these natural products of microbial and plant origin, including amino acids, stilbenes, alkaloids, polyketides, and phenylpropanoids such as flavonoids, creating natural product hybrids with altered or enhanced bioactivities.

### 2.1 Alkaloids

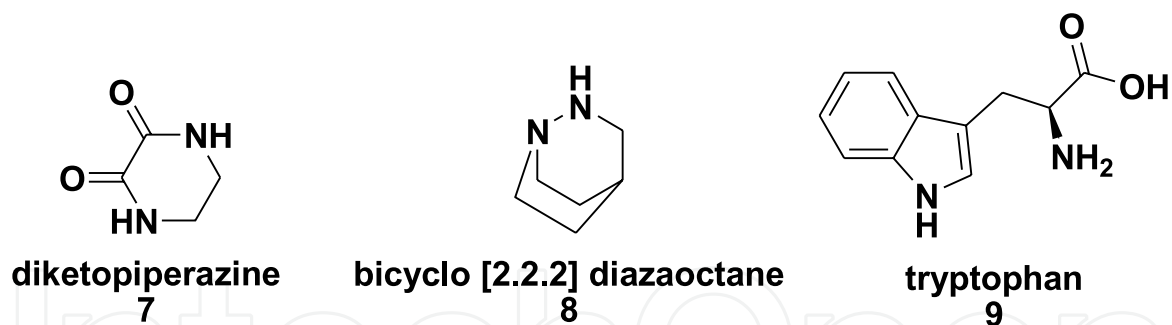
The term “alkaloid,” introduced in 1819 by the German chemist Carl Friedrich Wilhelm Meißner, is derived from Latin root *alkali* (which, in turn, comes from the Arabic *al-qalwi* meaning potassium-carbonate-containing ashes of plants). Heterocyclic nitrogen-containing compounds biosynthesized from amino acids can be termed as alkaloids, though for reasons historical and/or otherwise, there are many exceptions to this rule. Alkaloids represent one of the biggest classes of natural products, and due to the large number and structural diversity, they offer a vast field of investigation. Based on their biosynthetic precursor and heterocyclic ring system, alkaloids are classified into diverse categories (**Figure 1**), namely indole (**1**), purine (**2**), quinolone (**3**), isoquinoline (**4**), tropane (**5**), imidazole (**6**), etc. [9].

Prenylated indole alkaloids are a large family of secondary metabolites containing indole/indoline and isoprenoid moieties or structures derived thereof. These alkaloids generally contain a diketopiperazine (**7**) or a bicyclo [2.2.2] diazaoctane ring (**8**) as a core structure and are biogenetically derived from tryptophan (**9**) (**Figure 2**), a cyclic amino acid, and one or two isoprene units [10]. From filamentous fungi, especially from the genera *Penicillium* and *Aspergillus*, numerous prenylated indole alkaloids including asperparalines (**10**), brevianamides (**11**), marcfortines (**12**), notoamides (**13**), paraherquamides (**14**), stephacidins (**15**), and versicolamides (**16**) (**Figure 3**) have been isolated [11]. They are attractive targets for chemical synthesis, biosynthesis, and biological activity studies due to the fact that they exhibit a diverse range of relevant biological activities such as insecticidal, cytotoxic, anthelmintic, and antibacterial properties.

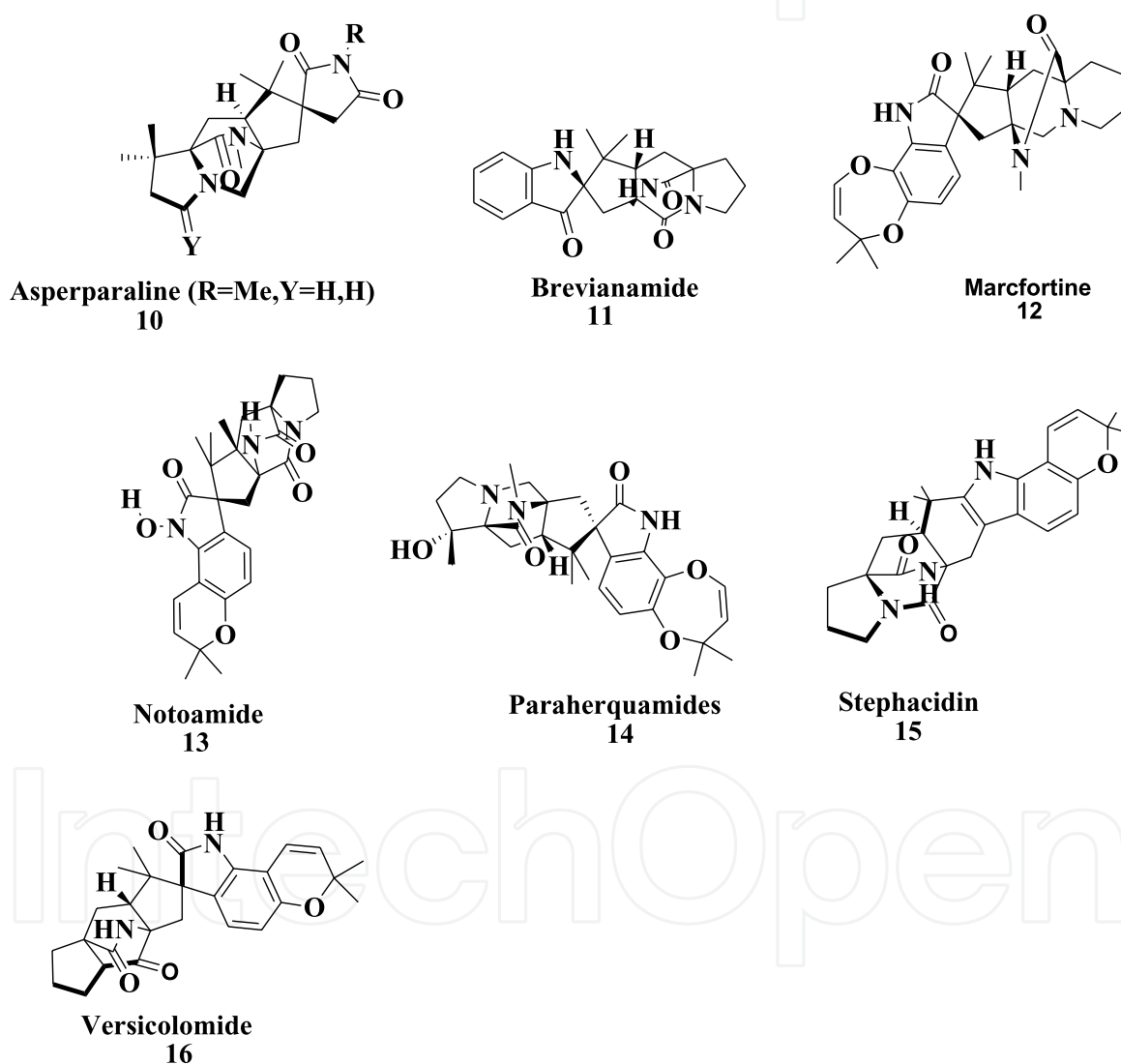
Asterriquinones (**17a** and **17b**) are a large group of the prenylated indole alkaloids containing two tryptophan moieties with a bis (indolyl) benzoquinone structure (**Figure 4**). They exhibit remarkable pharmacological activities such as antiretroviral,



**Figure 1.**  
*Diverse categories of alkaloids.*



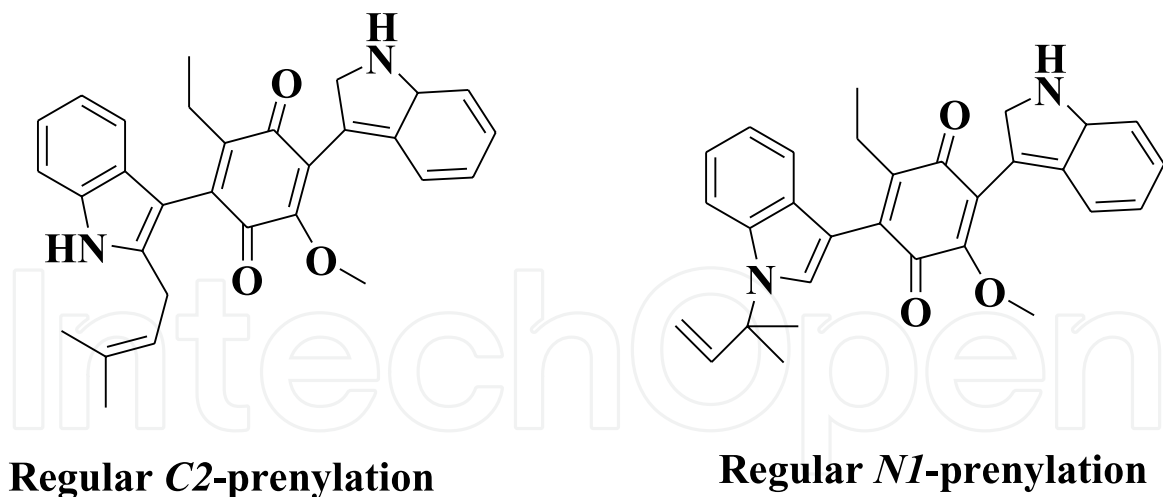
**Figure 2.**  
*Prenylated indole alkaloids core structure.*



**Figure 3.**  
*Different classes of prenylated indole alkaloids.*

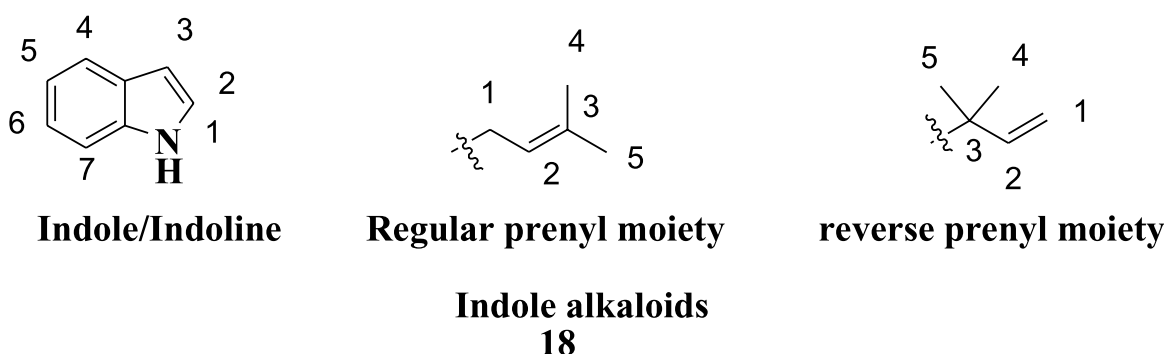
antitumor, and antidiabetic properties [12]. In prenylated indole alkaloids (18), the prenyl moiety is connected at either C1 or C3 to an aromatic nucleus, which are referred to as regular or reverse prenylation, respectively (Figure 5).

Prenylated purine alkaloids isolated from the seeds of *Gleditsia japonica* have been identified as prenylated purine alkaloid glucosides and named as the locustoside (19) (Figure 6). The plant cytokinin N<sup>6</sup>-isopentenyladenine (20) (Figure 7) and



### Asterriquinones 17 a 17 b

**Figure 4.**  
 Asterriquinones with a bis (indolyl) benzoquinone structure.

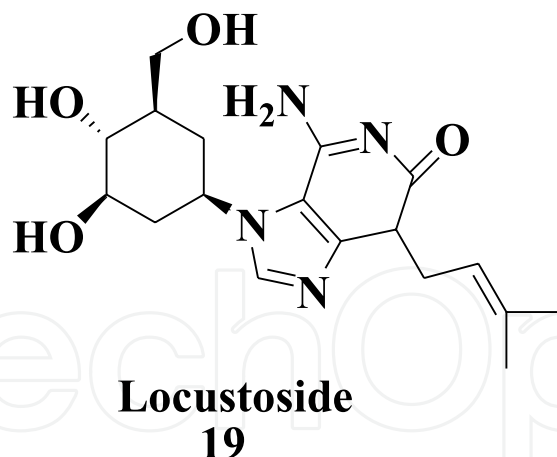


**Figure 5.**  
 Regular or reverse prenylation of indole alkaloids.

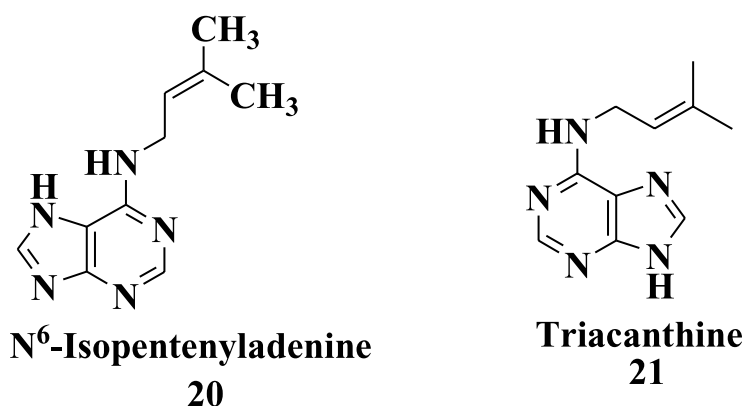
$N^3$ -prenylated purine alkaloids, e.g., triacanthine (21) (Figure 7), from the leaves of *Gleditsia triacanthos* have been reported [13, 14]. Triacanthine (21) shows hypertensive activity, also cardiotoxic, antispasmodic, and a respiratory analeptic. It has also been reported to exert antitumor effects in bladder cancer in vitro and in vivo [15]. The cytokinin,  $N^6$ -( $\Delta^2$ -isopentenyl) adenine, is found to be 3.3 times as active as  $N^6$ -( $\Delta^2$ -isopentenyl) adenosine in promoting the growth of cytokinin-requiring tobacco (*Nicotiana tabacum*) callus [16].

Prenylated quinolinone alkaloids, aspoquinolones (22, 23) (Figure 8), and prenylated isoindolinone alkaloids, aspernidines (24, 25, 26) (Figure 8), have been isolated and characterized from the fungus *Aspergillus nidulans*. These compounds exhibit varied cytotoxicity against various human cancerous cells. Aspoquinolones differ at the configuration of cyclopropyl ring pointing to the fact that the specific configuration of the cyclopropyl ring is essential for their cytotoxic activity [17].

Prenylated alkaloids isolated from plants and fungi are a good example of high structural diversity from only a limited array of structurally nondiverse starting materials. The assembly of complex carbon skeletons is mediated by enzyme catalyzed selective C–H oxidation reactions. The ambivalent reactivity of the



**Figure 6.**  
*Prenylated purine alkaloid.*



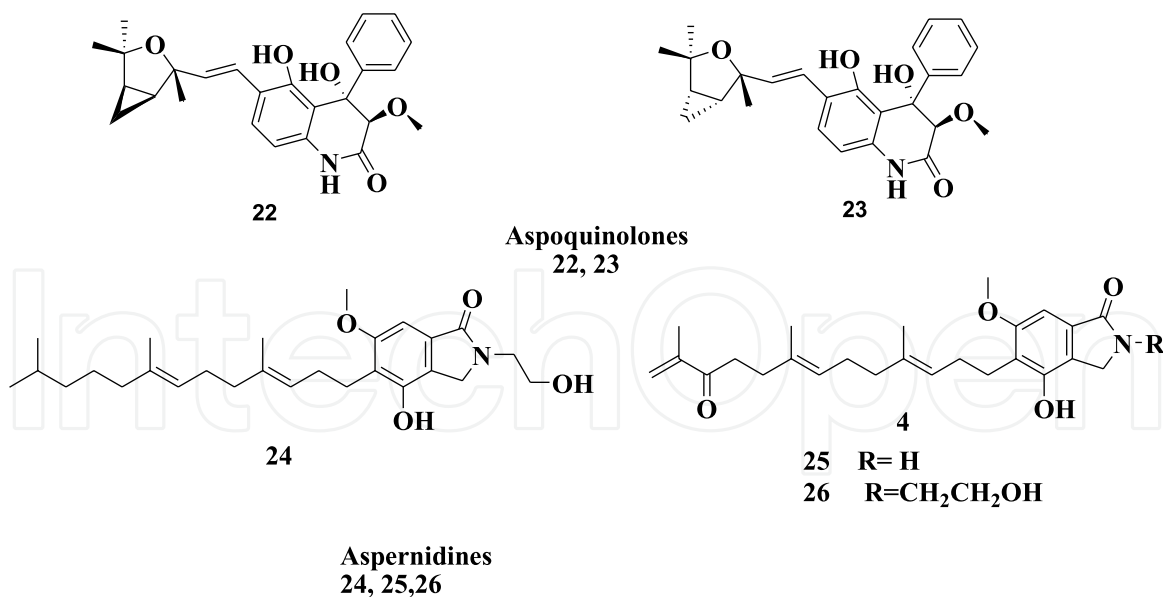
**Figure 7.**  
*N<sup>6</sup> and N<sup>3</sup> -prenylated purine alkaloids.*

heteroatom is exploited in the diverse condensation chemistry during the prenylated alkaloid biogenesis [18].

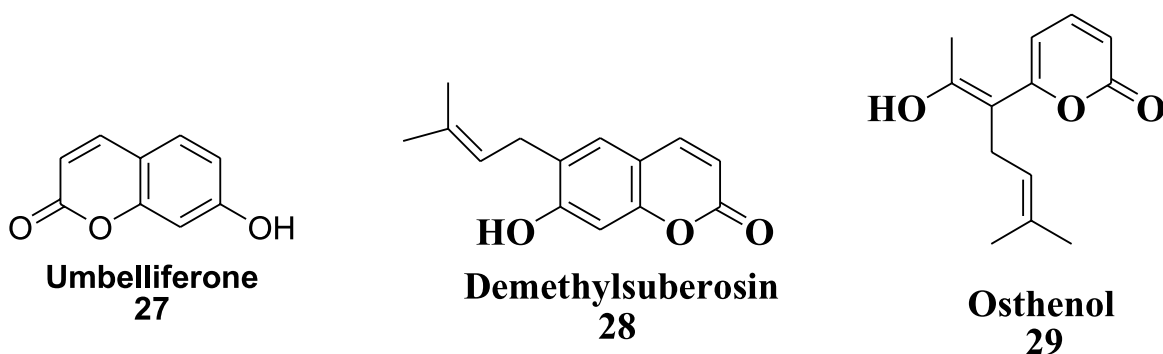
## 2.2 Phenylpropanoids

A diverse family of secondary metabolites synthesized by plants, bacteria, and fungi from the amino acids phenylalanine and tyrosine are termed as phenylpropanoids. The term “phenylpropanoid” is generally used to refer to any compound bearing a 3-carbon propene chain attached to 6-carbon aromatic phenyl ring (C6-C3 compounds). Most of the phenylpropanoids are formed from cinnamic or *p*-coumaric acids. Several pharmacological activities including antimicrobial, antioxidant, anti-inflammatory, antidiabetic, and anticancer activities have been attributed to these diverse groups of compounds that can be found to be present in spices, herbs, fruits, vegetables, and cereal grains. Owing to their antioxidant property, they exhibit renoprotective, neuroprotective, cardioprotective, and hepatoprotective effects [18].

The prenylations of umbelliferone (27) in the 6 or 8 position yield demethylsumberosin (28) and osthénol (29) (**Figure 9**) and give access to the branch pathways to linear or angular furano and pyranocoumarins, which are predominantly found in the *Umbelliferae* [19]. The hydrolysis of the secondary signal messengers’ cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) is catalyzed



**Figure 8.**  
 Prenylated quinolinone alkaloids (22, 23) and isoindolinone alkaloids (24, 25, 26).



**Figure 9.**  
 Prenylated umbelliferone.

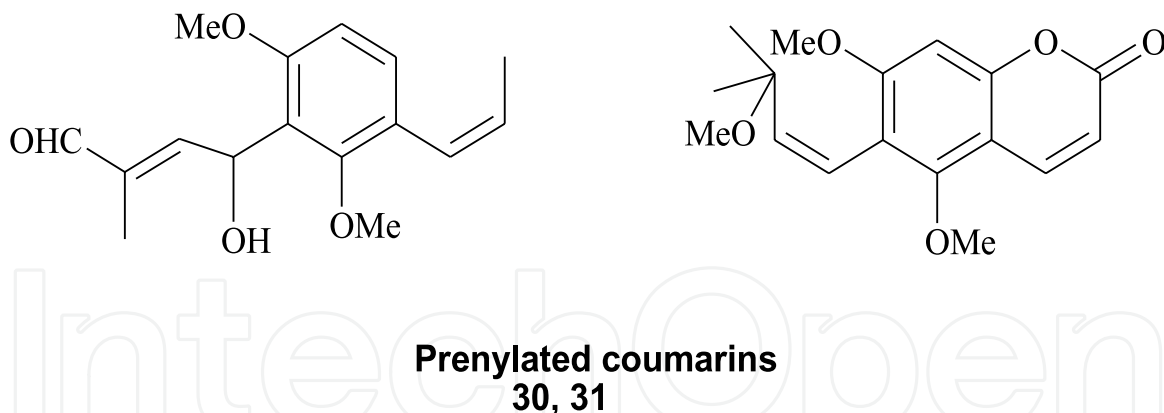
by the phosphodiesterases (PDEs). PDE inhibitors are therapeutic targets of high interest for central nervous system (CNS), inflammatory, and respiratory diseases. The prenylated coumarins (30, 31) from *Toddalia asiatica* (Figure 10) exhibit wide range of inhibition against the PDEs [20].

Marianins are the prenylated phenylpropanoids, isolated from the fungus *Mariannaea camptospora*. Marianin A (32) is a 5-methylcoumarin bearing two prenyloxy groups, whereas Marianin B (33) is an orcinol derivative substituted with a 3, 3-dimethyl-4-pentenoyl chain (Figure 11). Marianins show a weak antimicrobial activity and lack any significant anticancerous activity [21].

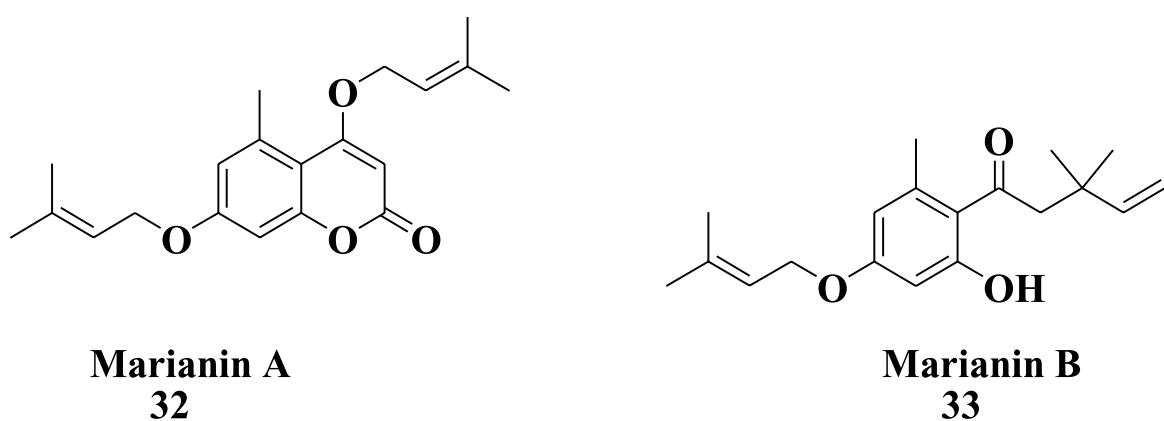
Flavonoids are valuable natural phenylpropanoids products and widely distributed in the plant kingdom bestowing a self-defensive strategy to the plants. Flavonoids are categorized on the basis of their oxidative states and substituents, into chalcones (34), flavones (35), flavanones (36), isoflavones (37), dihydroflavonols (38), anthocyanidins (39), etc. [22]. Flavonoids consist of C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub> skeleton with two aromatic rings A and B and a (dihydro) benzopyran ring C adjacent to A (Figure 12).

Prenylation at the two benzene rings, or  $\alpha$ ,  $\beta$  carbons in chalcones while enhancing the structural diversity, increases their bioactivities as well. The cytotoxic activity of the 3-hydroxylated derivative of xanthohumol (40) is much higher than its





**Figure 10.**  
*Prenylated coumarins.*



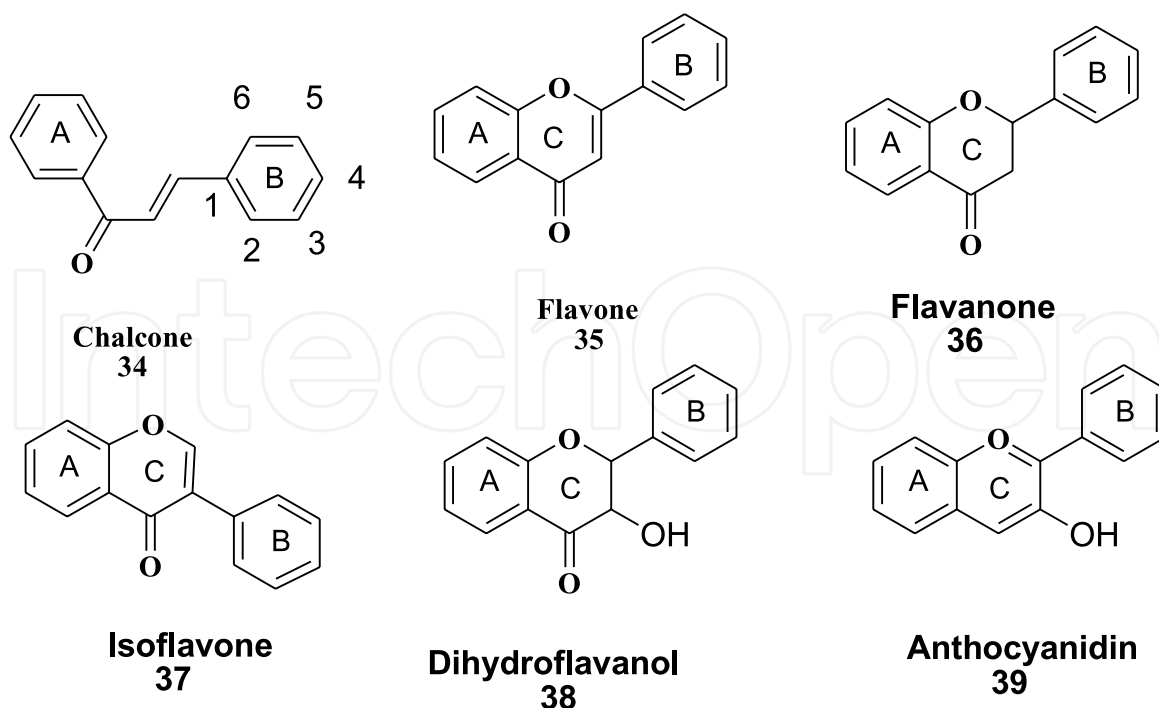
**Figure 11.**  
*Prenylated phenylpropanoid.*

nonprenylated analogue 3-hydroxyhelichrysetin (**41**) (**Figure 13**). Diverse biological and pharmacological activities such as antimicrobial and antiviral (C5-prenylated derivatives), antioxidant (the C–H bonds of the prenyl substituents are the most thermodynamically preferred sites for free radical attack, and thus play an important role in the antioxidant activity) cytotoxic, chemopreventive, and estrogenic activities are attributed for prenylated chalcones [23].

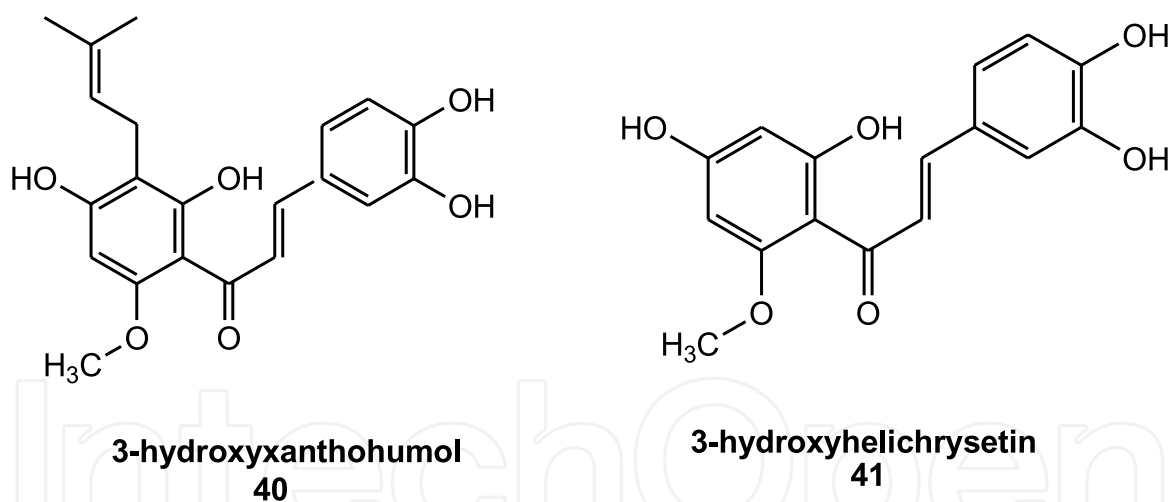
The success of cancer therapy is largely impeded by the development of multi-drug resistance (MDR) by tumor cells. The MDR conferred to the cancer cells by the overexpression of the P-glycoprotein (Pgp) [24]. In comparison to the flavanones, isoflavones, and glycosyl derivatives, chalcones, flavones, and flavonols bind more strongly to Pgp cytosolic site. For the ability of these modulators to mimic the adenine moiety of ATP, the hydroxylation at position 5 is essential, in addition to the presence of a ketone at position 4 [25]. Interestingly, the modulating effects of C-prenylated derivatives produced by nontoxic concentrations suggest that these compounds should be investigated in vivo as potential Pgp modulator in tumor cells.

### 2.3 Polyketides

Polyketides are produced by bacteria, fungi, plants, and few marine organisms. These secondary metabolites exhibit a high degree of structural diversity, even though they are synthesized from simple acyl building blocks. They form a chain of either



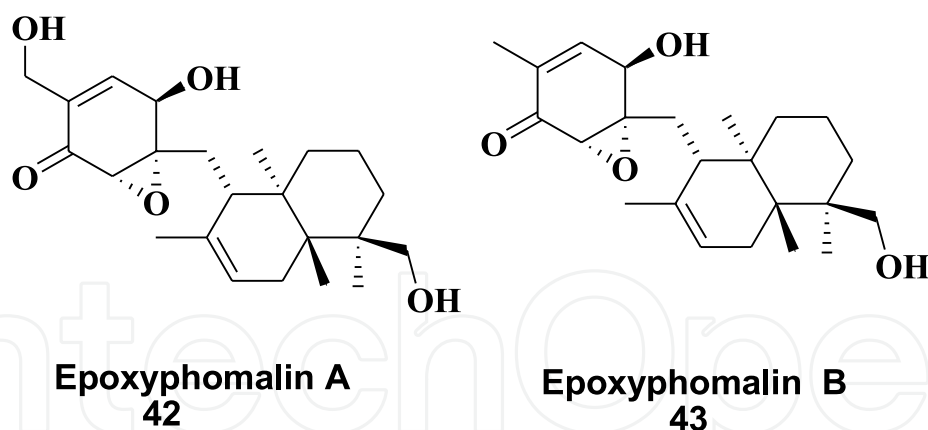
**Figure 12.** Flavonoids with C6-C3-C6 skeleton with two aromatic rings A and B and a (dihydro) benzopyran ring C adjacent to A.



**Figure 13.** Prenylated chalcone, 3-hydroxylated derivative of xanthohumol (40) and its nonprenylated analogue 3-hydroxyhelichrysetin (41).

alternating ketones or reduced ketones and methylene groups. Polyketides, owing to their structural diversity and acute toxicity, find applications in medicine, agriculture, and industry. The substitution with prenyl moieties either at a carbon atom of the polyketide nucleus or connection via an ether linkage is a prominent feature in most of these metabolites.

Epoxypomalins A and B (42, 43) (Figure 14) are the prenylated polyketides isolated from marine fungi *Phoma* sp and have strong cytotoxic properties toward six cancer cell lines [26]. Arugosins G and H (44, 45) (Figure 15) are prenylated polyketides isolated from marine fungus *Emericella nidulans* var. *acristata*. Arugosin H may be derived from chrysophanol anthrone, which undergoes oxidative cleavage



**Figure 14.**  
Prenylated polyketides—Epoxyphomalins.

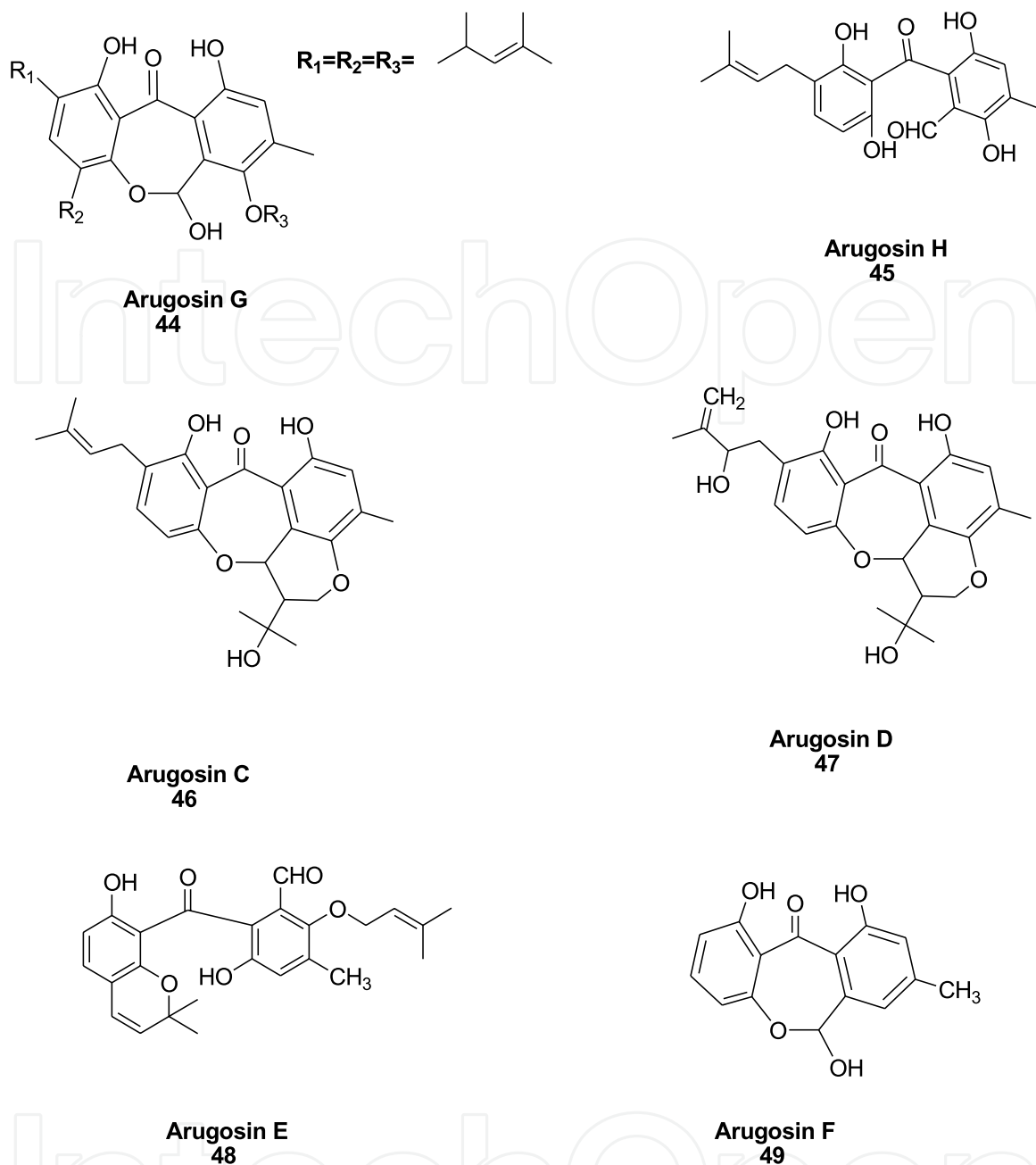
to form the aldehyde function, followed by C-prenylation and hydroxylation. The aldehyde function can be converted to a hemiacetal function, as seen in the tricyclic arugosin G. Arugosins C, D, E (46, 47, 48) (Figure 15) also occur in *Aspergillus* spp., whereas arugosin F (49) is found in *Ascodesmis sphaerospora* [27].

Prenylated phenyl polyketides named peplidiforones A–D (50, 51, 52, 53) (Figure 16) are isolated and characterized from *Hypericum peplidifolium*. Unusual carbon skeleton consisting of a furan ring substituted by a 2, 2-dimethylbut-3-enoyl moiety possessed by Peplidiforone C (52) is the first example of a prenylated furan derivative isolated from the genus *Hypericum*. The peplidiforones are reported to possess antimicrobial, cytotoxic, antidepressive, antioxidant, and anti-inflammatory effects [28].

Three novel and unusual prenylated polyketides, namely oumarone (54), bissaone (55), and aissatone (56) (Figure 17), have been isolated from *Harrisonia abyssinica* [29]. Extracts of the bark and the root of this plant exhibit in vitro antiviral, antibacterial, antifungal, and molluscicidal activities [30].

## 2.4 Terpenoids

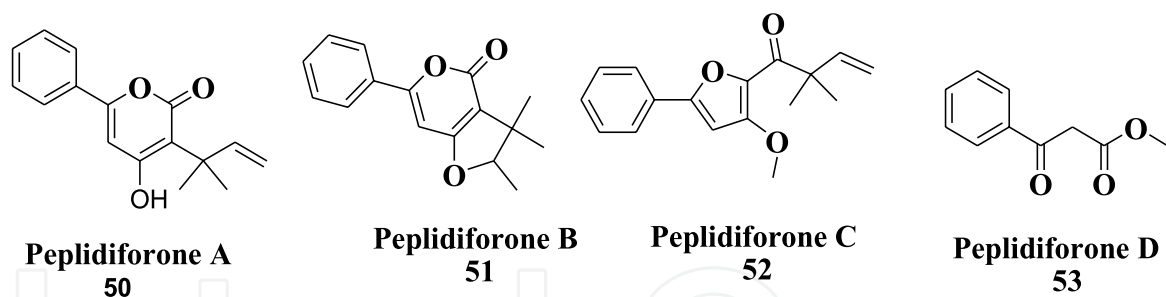
The organic compounds derived from the 5-carbon compound isoprene (57) and their polymers known as terpenes are collectively called as terpenoids. They are produced by various genera of plants, algae, sponges, and fungi. Terpenoids constitute about 60% of the secondary metabolites produced by plants, known till date. Due to their broad spectrum of medicinal applications, the terpenes have gained significant pharmaceutical value. Without clear distinction, the terms, terpene and terpenoid are usually used interchangeably in the literature. The tree resin terpenoid (German: Terpentin; Latin: *Balsamum terebinthinae*) contains a repeating hydrocarbon isoprene unit as a monomer. The etiology of the term “terpene” stems from this tree resin [31]. Generally, in a live plant one can find a terpene, whereas the terpene upon modification with different functional groups and addition or removal of oxidized methyl group makes it a terpenoid. The biological activity of the terpenoids depends on the variation in their structures. The structural unit of a terpene and terpenoid is a five-carbon unit called isoprene (57). These isoprene units are arranged in head-to-head, head-to-tail, and tail-to-tail fashion to give different terpenoids, namely monoterpenes (58), sesquiterpenes (59), diterpenes (60), sesterpenes (61), and triterpenes (62) etc. (Figure 18) [32].



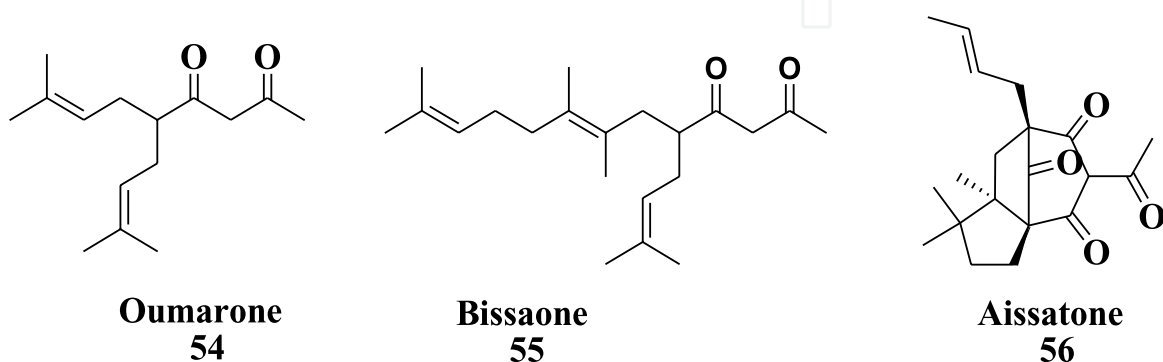
**Figure 15.**  
 Prenylated polyketides—Arugosins.

About 1000 prenylated phenolic composite-type terpenoid compounds have been identified to date in plants. The prenylated flavonoids constitute the active components of various medicinal plants. They show sustained biological activities in humans and therefore have been actively investigated as pharmaceuticals [33]. Coumarin derivatives are a group of lactonized phenylpropanoids. The isoprenoid units are not seen in the basic structure of the Furanocoumarins (FCs); therefore the FCs, which are a subgroup of coumarin core with an attached furan ring, are not generally recognized as terpenoid derivatives. However, their furan rings are derived from prenyl chains, followed by the cleavage of a C3 unit to yield the atypical terpenoid derivatives [34].

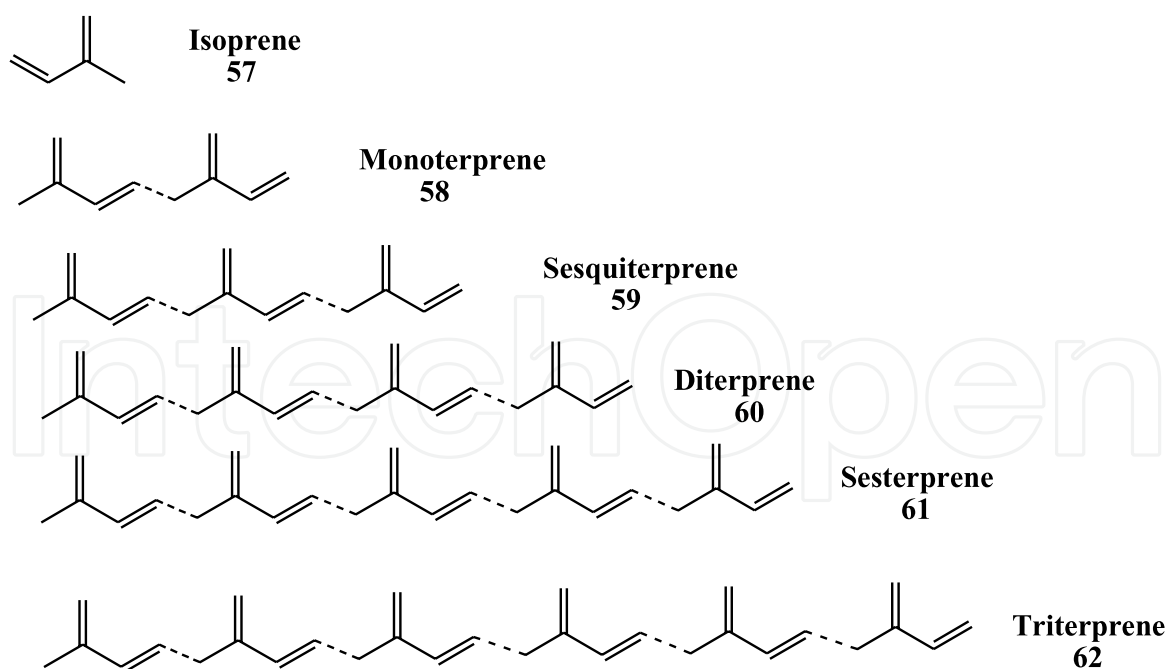
Two rare antioxidative prenylated terpenoids from loop-root Asiatic mangrove *Rhizophora mucronata* have been isolated. These terpenoids include one new prenylated guaiane sesquiterpenoid (**63**) with an uncommon five-membered lactone ring



**Figure 16.**  
*Prenylated phenyl polyketides—Peplidiforones.*

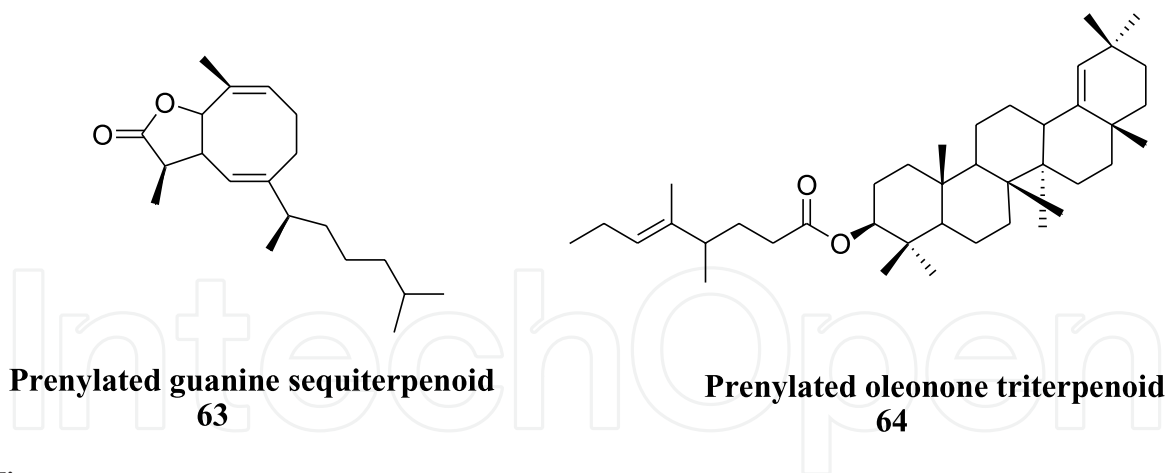


**Figure 17.**  
*Unusual prenylated polyketides.*



**Figure 18.**  
*Different classes of terpenoids.*

and prenylated oleanane-type triterpenoid (64) (Figure 19). These prenylated terpenoids have a potential as lead molecules for use in pharmaceutical and functional food industries [35].



**Figure 19.**  
*Rare antioxidative prenylated terpenoids.*

### 3. Prenyltransferases (PTs)

All those enzymes that catalyze the transfer of prenyl groups to a wide variety of acceptors such as proteins, isoprenoid groups, aromatic compounds, etc., are termed as prenyltransferase (PT). PTs are distributed widely in all the living kingdoms and participate in a variety of the metabolic routes [36]. Of late, with increased interest in isoprenoid chemistry, PTs have gained more recognition. The importance of prenylation for the regulation and targeting of bioactive compounds in the cell has been recognized. Among these, the farnesylation of proteins in signal transduction cascades involved in carcinogenesis has been very prominent instance [37].

PTs are unique enzymes in that, apart from creating new C–C bonds, they are also successful in introducing a double bond in the end product. The activation as well as enhancement of the biological activity is generally associated with such features. PTs are peculiar enzymes because they not only create a new C–C bond, a reaction that only some aldolases and lyases have been previously used for [38], but also introduce a double bond in the framework of the final product, a feature that is often associated with the activation or the enhancement of biological properties [39].

The regiospecific/stereoselective chemical synthesis of prenylated aromatic compounds is an arduous task to achieve in good yield, besides the usage of protective groups. But the essential feature in a molecule to exhibit biological activity is its regiospecificity/stereoselectivity. Therefore, an interesting tool for the organic synthesis of biologically active compounds is by the possibility of manipulating enzymatic catalysts such as PTs.

Generally, depending upon the stereochemistry of the resulting products, PTs are divided into two classes, namely *cis* (or *Z*) and *trans* (or *E*). Dimethylallyltransferase is an example of *trans*-prenyltransferase, whereas dehydrodolichol diphosphate synthase is an example of *cis*-prenyltransferase.

The transfer of a C5 (dimethylallyl), C10 (geranyl), or C15 (farnesyl) prenyl group derived from the corresponding isoprenyl diphosphate metabolites onto a variety of electron-rich aromatic acceptors is catalyzed by aromatic prenyltransferases. By increasing the affinity for biological membranes and interactions with cellular targets, prenylation provides a higher level of bioactivity compared with the nonprenylated precursor [40]. In a Friedel-Crafts-like reaction, aromatic compounds such as hydroxybenzoic acids and hydroxyphenylketones are prenylated by phenol-oligoprenyldiphosphatase [41]. The

role of regiospecific catalysts in widening the horizon of diversity and biological activities of many classes of natural products both *in vivo* and *in vitro* has taken huge interest with recent identification of these enzymes.

#### 4. Conclusion

The prenylated natural compounds exhibit a broad spectrum of interesting molecular, biological, and pharmacological activities. There is a definite consonance between the structure-activity relationship and bioactivities of prenylated natural compounds. The prenyl-moiety increases the chemical diversity and makes the backbone compound more lipophilic, which leads to its high affinity with cell membranes. The prenylation enhances the antibacterial, anti-inflammatory, antioxidant, cytotoxicity, larvicidal as well as estrogenic activities of several natural compounds. Therefore, to fully explore the health-promoting potential, more research is required in the future. Especially the prenyl groups seem to be crucial for the anticancer activity of the natural compounds, possibly leading to enhanced cell membrane targeting and thus increased intracellular activity. Today, cancer prevention is an increasingly important social issue, and the identification and characterization of dietary components or natural products with distinct cancer-preventive qualities and possibly even therapeutic properties, while bearing only low toxicity, are a promising research approach.

#### Abbreviations


PTases	prenyltransferases
DMATS	dimethylallyl tryptophan synthase
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
PDEs	phosphodiesterases
CNS	central nervous system
MDR	multidrug resistance
Pgp	P-glycoprotein

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